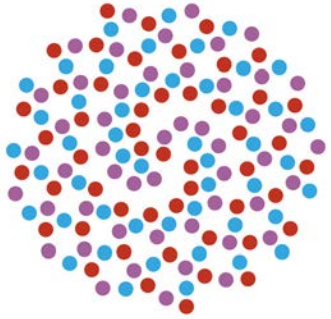

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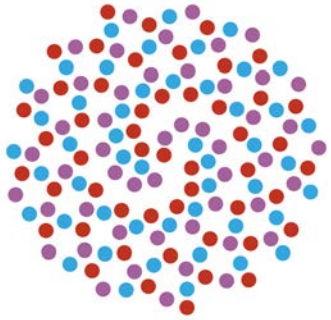
Slides are from Level 3 Biology Course Content Day, 7th November 2012

Presenter: Professor Peter Shepherd



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Background

The Maurice Wilkins Centre is one of 7 Centers of Research Excellence (CoREs)

Named after Maurice Wilkins who was a New Zealand born scientist who won the Nobel prize together with Watson and Crick

MWC focuses on linking fundamental research of disease mechanisms with the development of therapeutic outcomes

MWC covers many scientific disciplines and consists of a network of more than 100 scientists spread throughout New Zealand

The main areas of focus are cancer, diabetes and infectious diseases.

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Teacher Fellowships at Queenstown Research Week

Queenstown research week is New Zealands biggest scientific meeting with over 700 scientist attending (including more than 100 from overseas)

MWC provides up to 4 fellowships covering conference registration, travel costs and accommodation

2013 dates are 26-28th August

Will be advertised in Gazette and also through our email network (if you leave your email address then we will notify you)

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Teacher Out Reach Days

Today is our first teacher out reach day (thanks to Rachel Heeney for allowing us to be part of the day)

First one is focusing on content for the new curriculum and slides from todays presentations will be available for all teachers who want them

We would like to do more but need feedback as to where scientists can help. Do you need input on content ? Would you just like more updates on exciting new developments in science ?

Let us know what you think ?

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New !!
Scientist for a Week

The Maurice Wilkins Centre will sponsor a number of teachers to spend a week in a real research laboratory working on cancer, diabetes or immune system research.

MWC will provide travel costs and accommodation

This is a great chance to see what its like to work in a real research environment and to make contacts with scientists that will hopefully be of ongoing use in your teaching programme

Will be advertised in Gazette and also through our email network (if you leave your email address then we will notify you)

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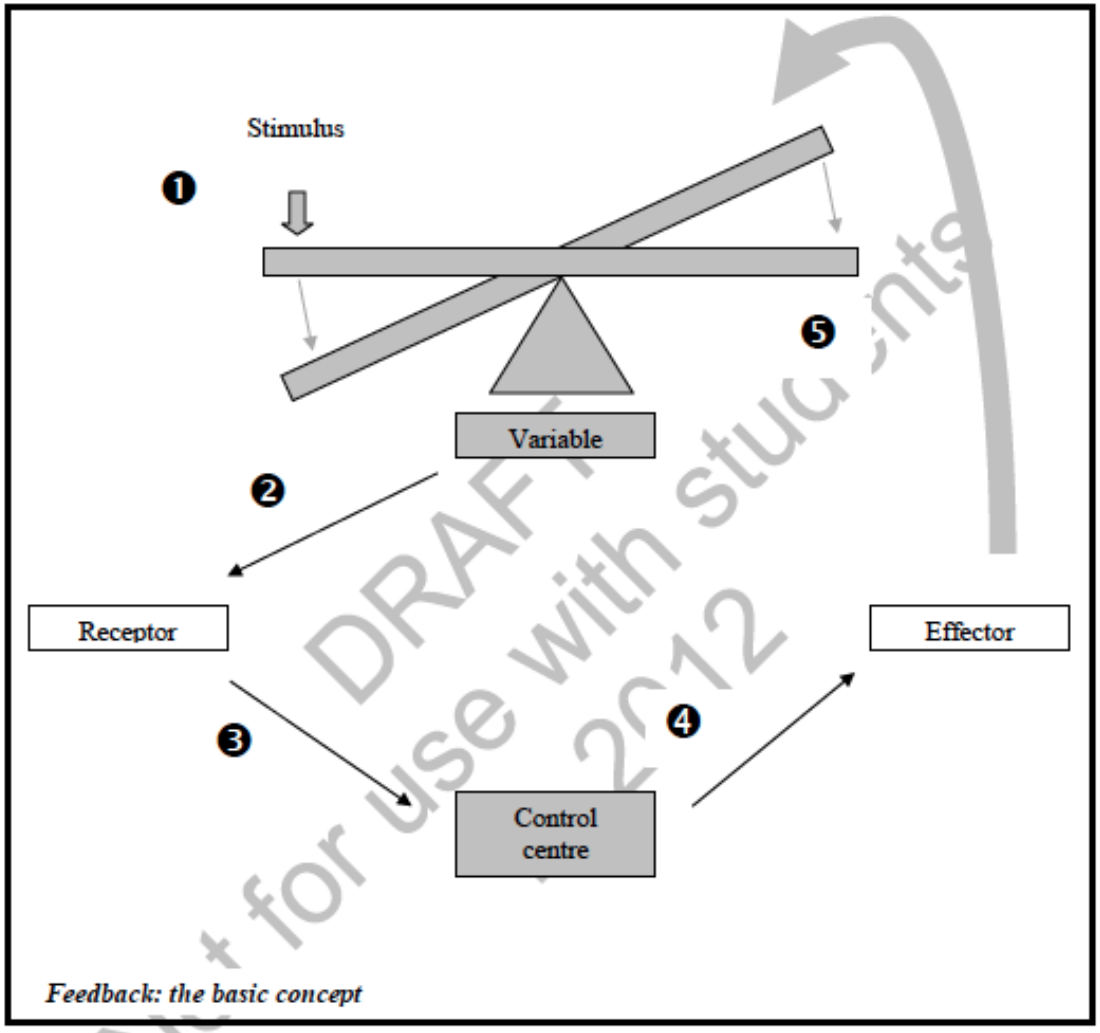
Glucose Homeostasis for Level 3 NCEA Biology

A sample of an NCEA Homeostasis Task

Student Resource A: Model of a generalised homeostatic system used by many animals



Examples of Criteria for Achievement Homeostasis

- Explain the purpose of the homeostatic mechanism
- Be able to explain the basis of the homeostatic mechanism
- Describe one way in which internal or external environmental factors can disrupt the homeostatic mechanism

Examples of Excellence Criteria for Homeostasis

- Be able to explain why it gives and adaptive advantage
- An explanation of the biochemical/biophysical pathways involved
- An analysis of how internal or external environmental factors can disrupt the homeostatic mechanism

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Part 1
What is homeostasis ?

Examples of homeostatic mechanisms are all around us

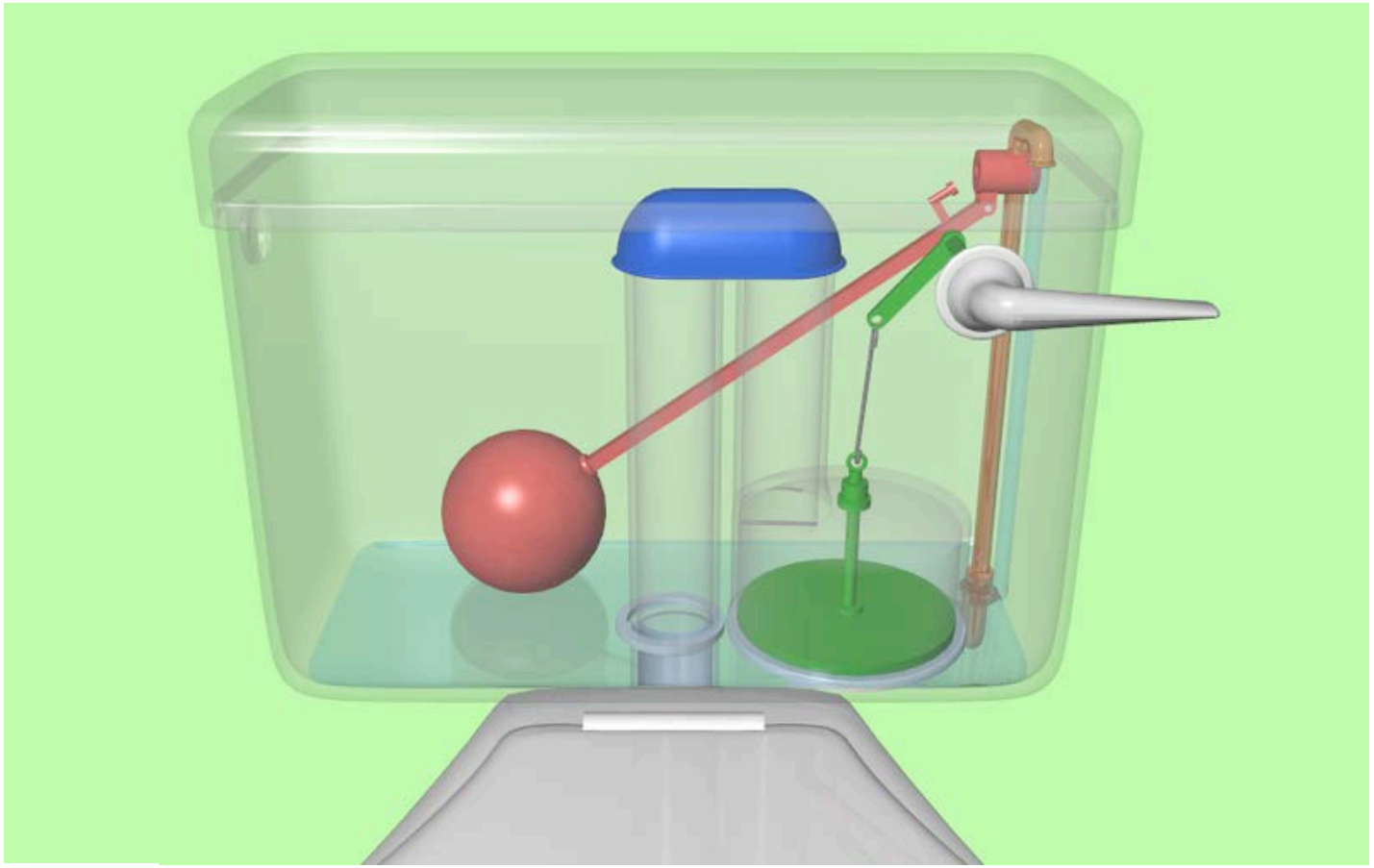
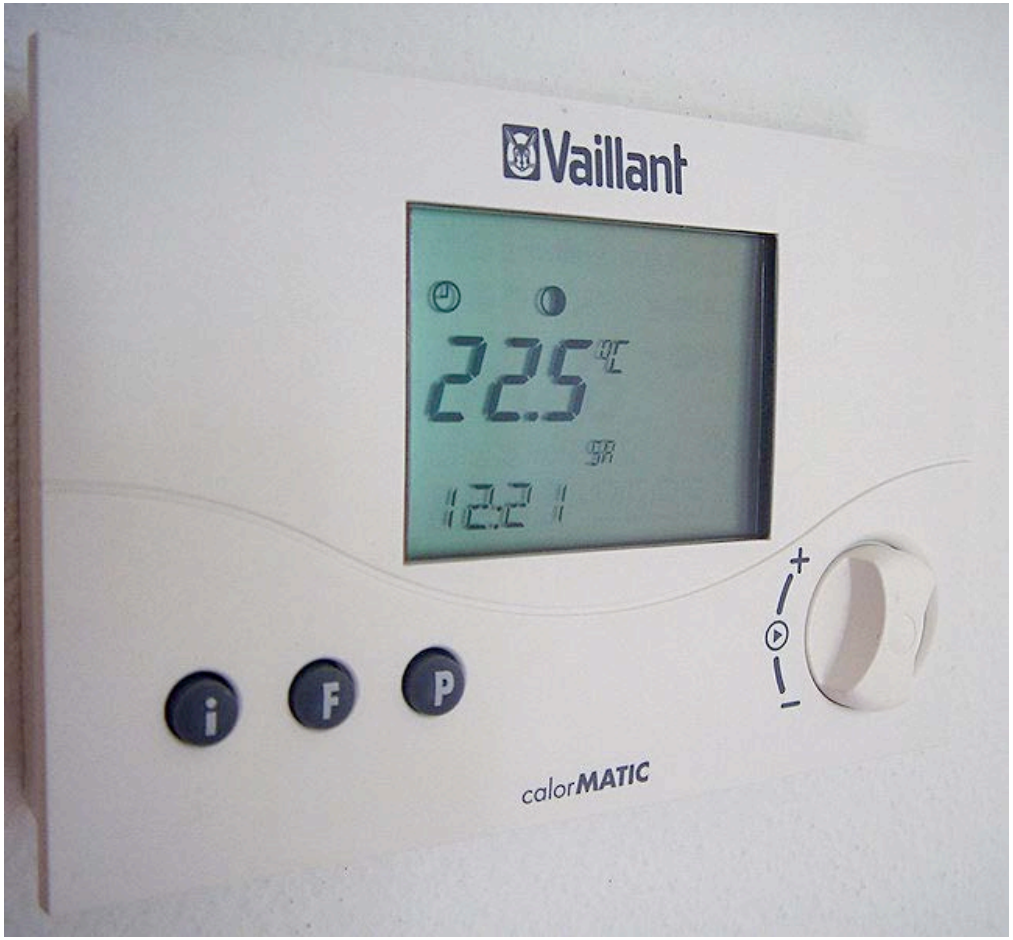


Image from Wikicommons

Examples of homeostatic mechanisms are all around us



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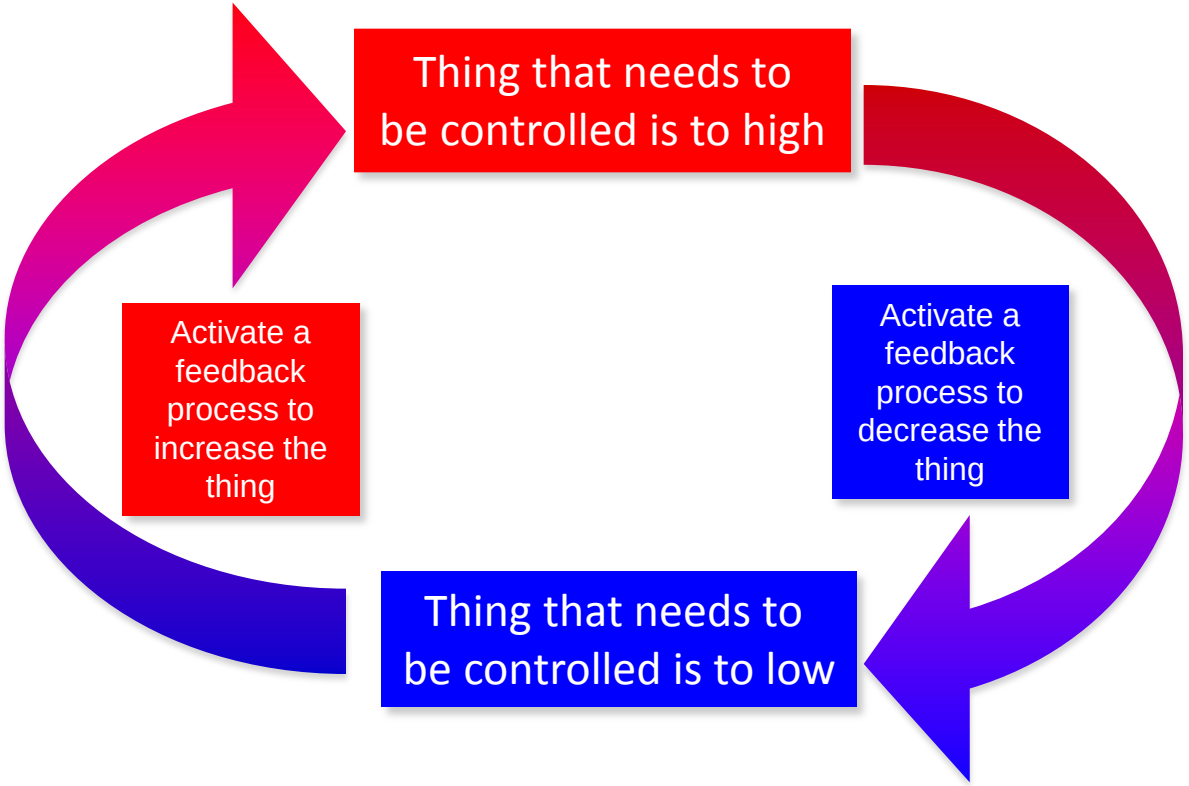
Homeostatic Mechanisms Use Feedback Loop



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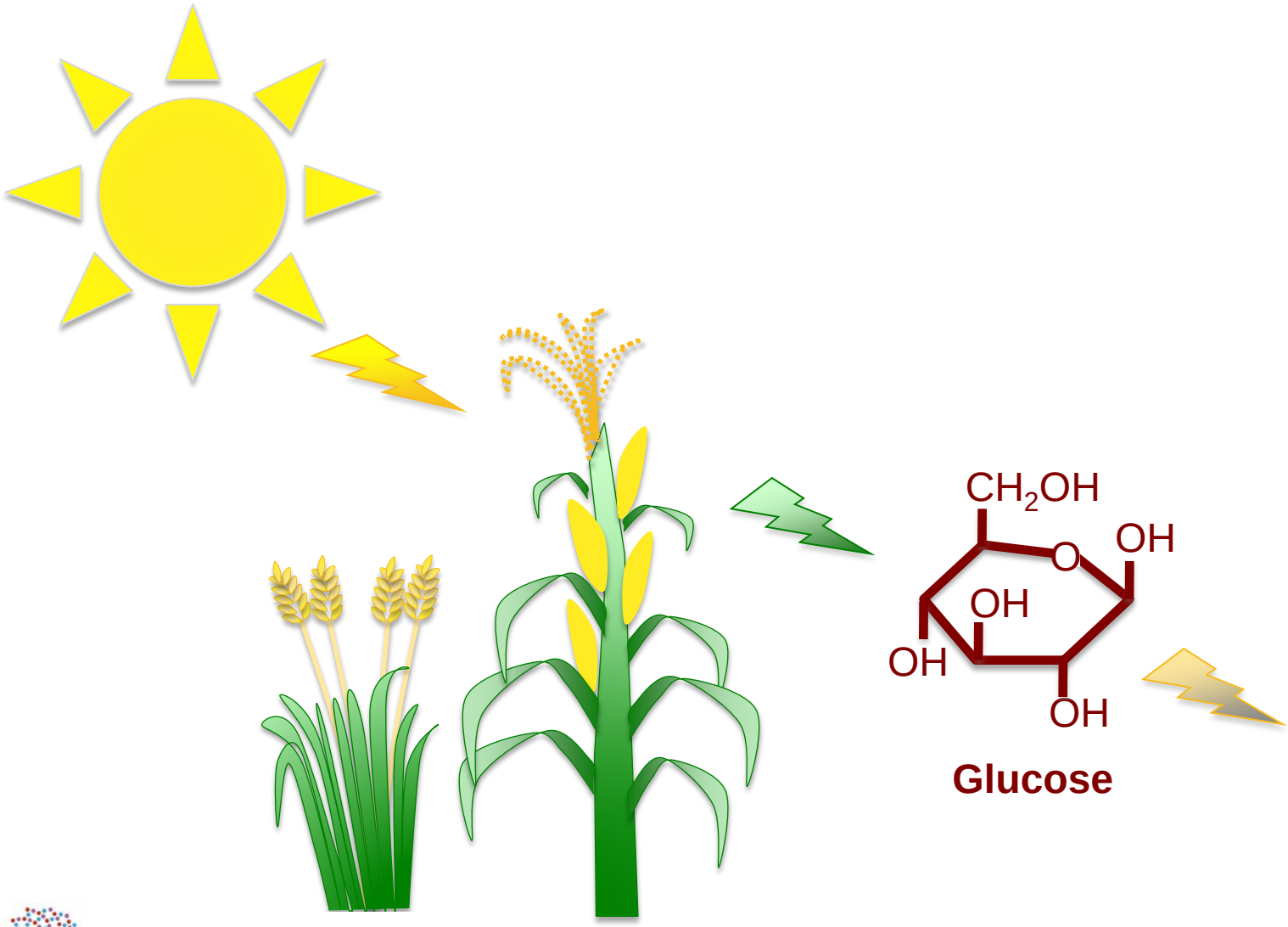
Part 2
Glucose homeostasis and how its regulated

Glucose is the Ultimate Biofuel



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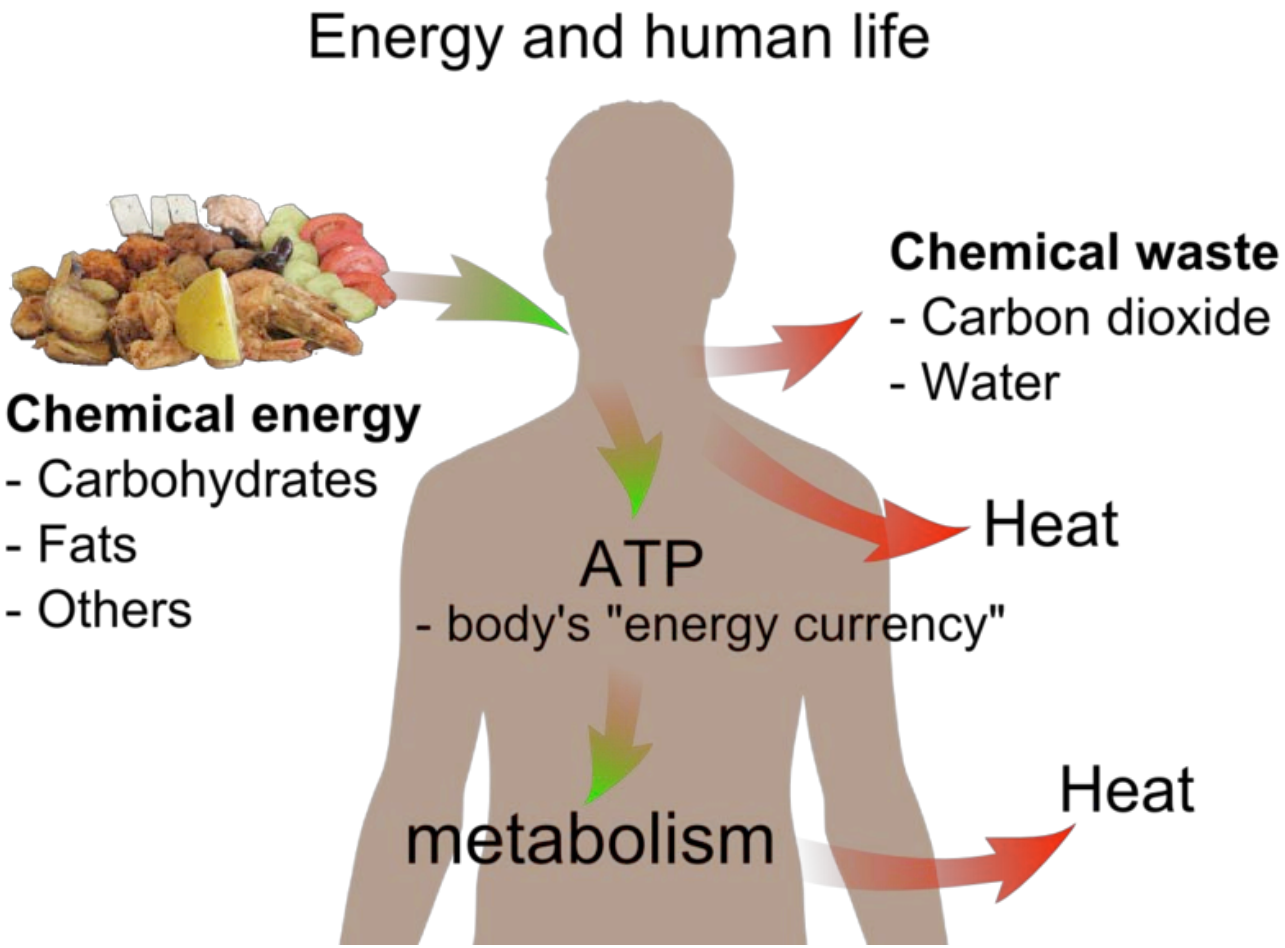


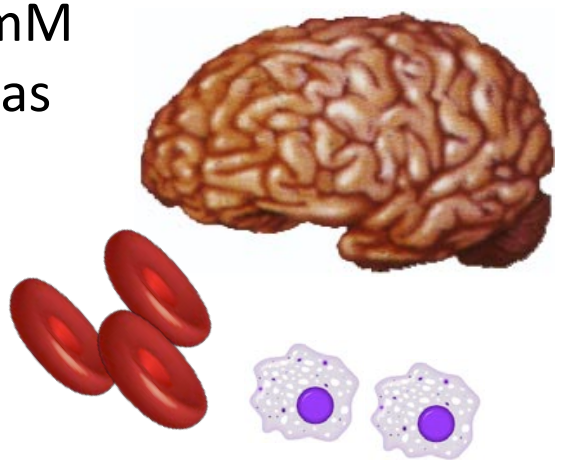
Image from Wikicommons

Glucose Homeostasis

Regulating blood glucose is important because:

The most important reason

- Some tissues can use a range of energy sources such as fats and even amino acids but several important tissues in the body can only really use glucose so these tissues have a need for a constant supply of glucose to function properly.
- These tissues includes red blood cells and immune cells
- Brain and the nervous system also rely on glucose which explains why when blood glucose levels fall below about 2.5 mM that people get seizures and can go into a coma as the brain doesn't function properly.
- Therefore maintaining a certain level of glucose is a matter of life and death.



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How Does Glucose get Into Cells

- Glucose can't get across the membrane of cells unless specific transporters are in the membrane to provide a channel for the glucose to move through.

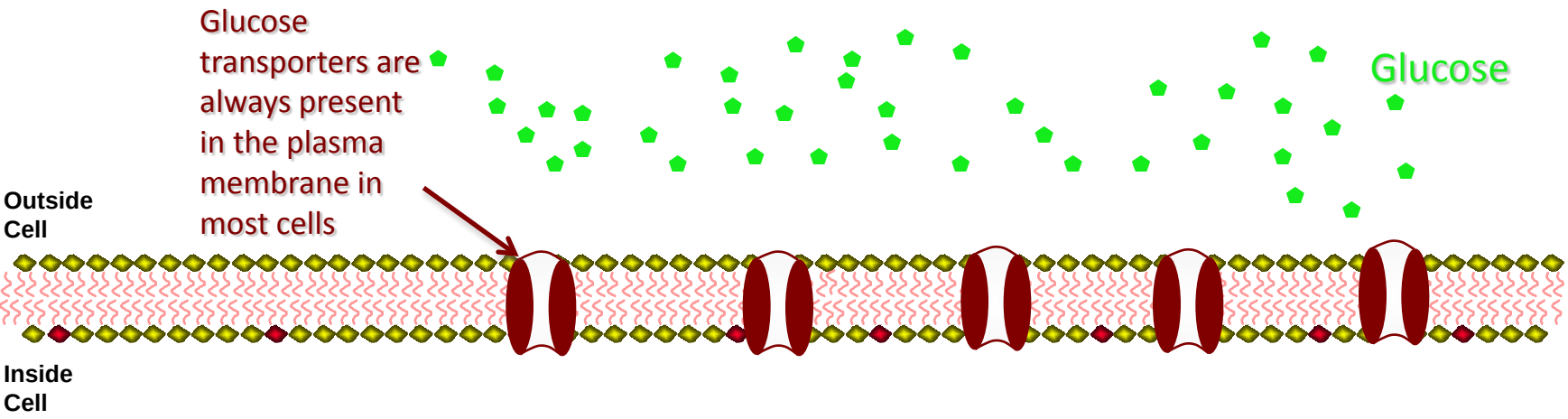
- These are specific for glucose and so are called glucose transporters. They do not use energy so will only transport glucose from areas of high glucose concentration to areas of low glucose concentration (i.e down a concentration gradient).

- Therefore if a cell is using glucose then levels in the cell drop and the glucose will move from the outside of the cell to the inside.

- In liver cells stimulated by glucagon there will be lots of glucose produced inside the cells from glycogen therefore the flow of glucose will be from inside the cell to the outside.

- In brain and liver there are always glucose transporters in the plasma membrane

How Glucose Uptake Works in Most Tissues Including Brain and Liver



The glucose flows from the area of high glucose concentration to the area of low glucose concentration until an equilibrium is reached

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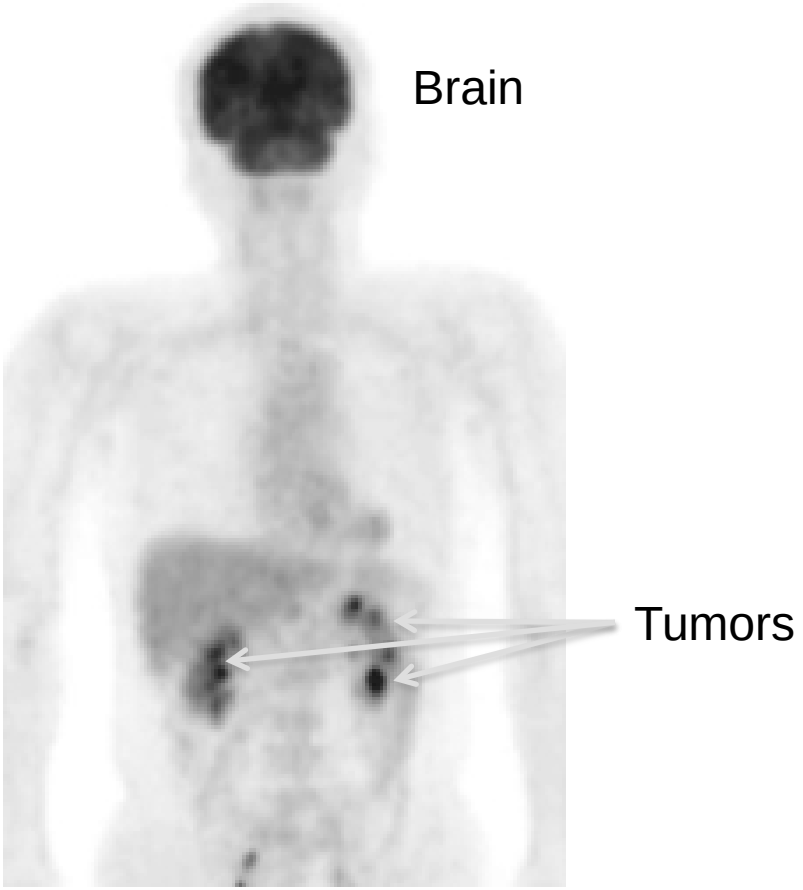
A Graphic Demonstration of How Much Glucose the Brain Actually Uses

- PET (Positron Emission Tomography) imaging is not a technique used by vets to scan animals but is a is a technique that uses radioactively labeled glucose to identify tissues in the body that use lots of glucose

- Tumors use a lot of glucose so it's a great way to locate tumors

- But it also shows just how much glucose the brain uses !



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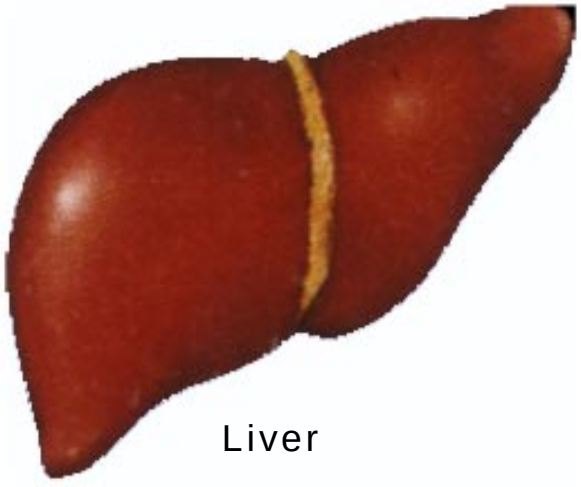
Regulating blood glucose is important because:

Next most important reason

- We need glucose all the time but we can't eat all the time so we need a system for storing glucose.
- So what is happening when blood glucose levels fall after a meal is that we are storing the glucose so that we can use it later
- The main place we store glucose is in the liver and we can store enough there to keep us going for 2-3 days.



Liver

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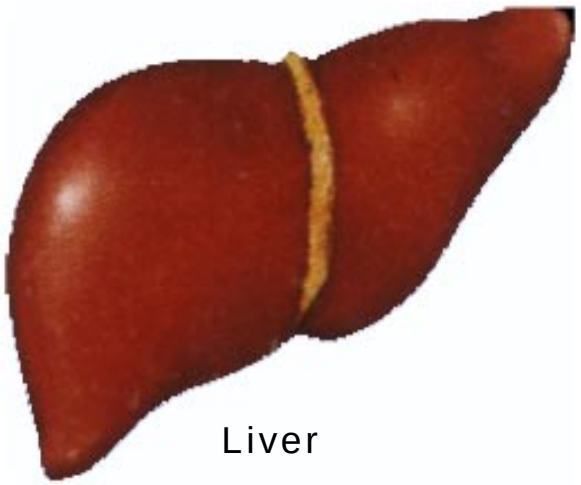
One of the livers roles is to be a “rechargeable glucose battery”



Liver

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Regulating blood glucose is important because:

Another very good reason

- High levels of glucose over a long term are dangerous because glucose can bind directly to proteins in the circulation by non-enzymatic means (a process called glycation) and cause damage to them.
- In the short term we won't die if blood glucose levels are to high and we won't even feel anything to tell us blood glucose is to high. However over a number of years high blood glucose levels will cause a lot of damage to cells in the body so its very important that the body keeps blood glucose levels at safe level.

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Measuring the amount of glycation on proteins can be a useful tool for measuring blood glucose levels over longer time periods

- The amount of glycation of proteins in the circulation is proportional to the amount of glucose that has been in the circulation.

- Glucose levels in the blood go up and down quite quickly so measuring blood glucose at a random time point doesn't really provide us a measure of how much glucose there has been in the circulation but by measuring the glycation of proteins we get an integral measure of glucose levels in the blood over the longer time frame.

- There is a lot of hemoglobin in the blood so looking at glycation of hemoglobin is a good way to do this, especially as the half life of hemoglobin is 14 days. The designation for the glycated hemoglobin that we measure is hemoglobinA1C (HbA1C) and this is often used to measure how much glucose has been in the blood over a period of 2 weeks or so. If more than 5% of hemaglobin is in the form of Hba1C then its concerning.

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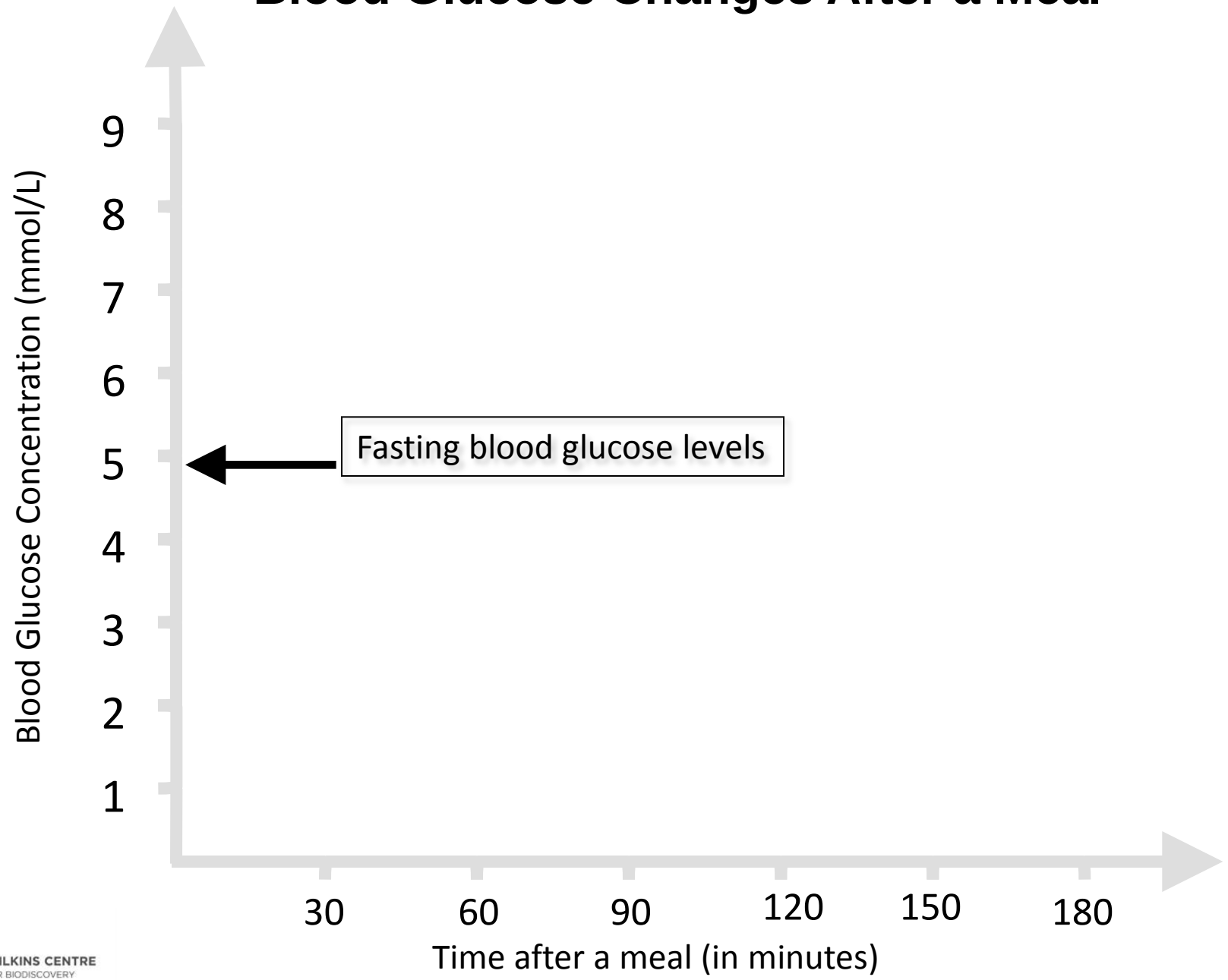
Blood Glucose Changes After a Meal



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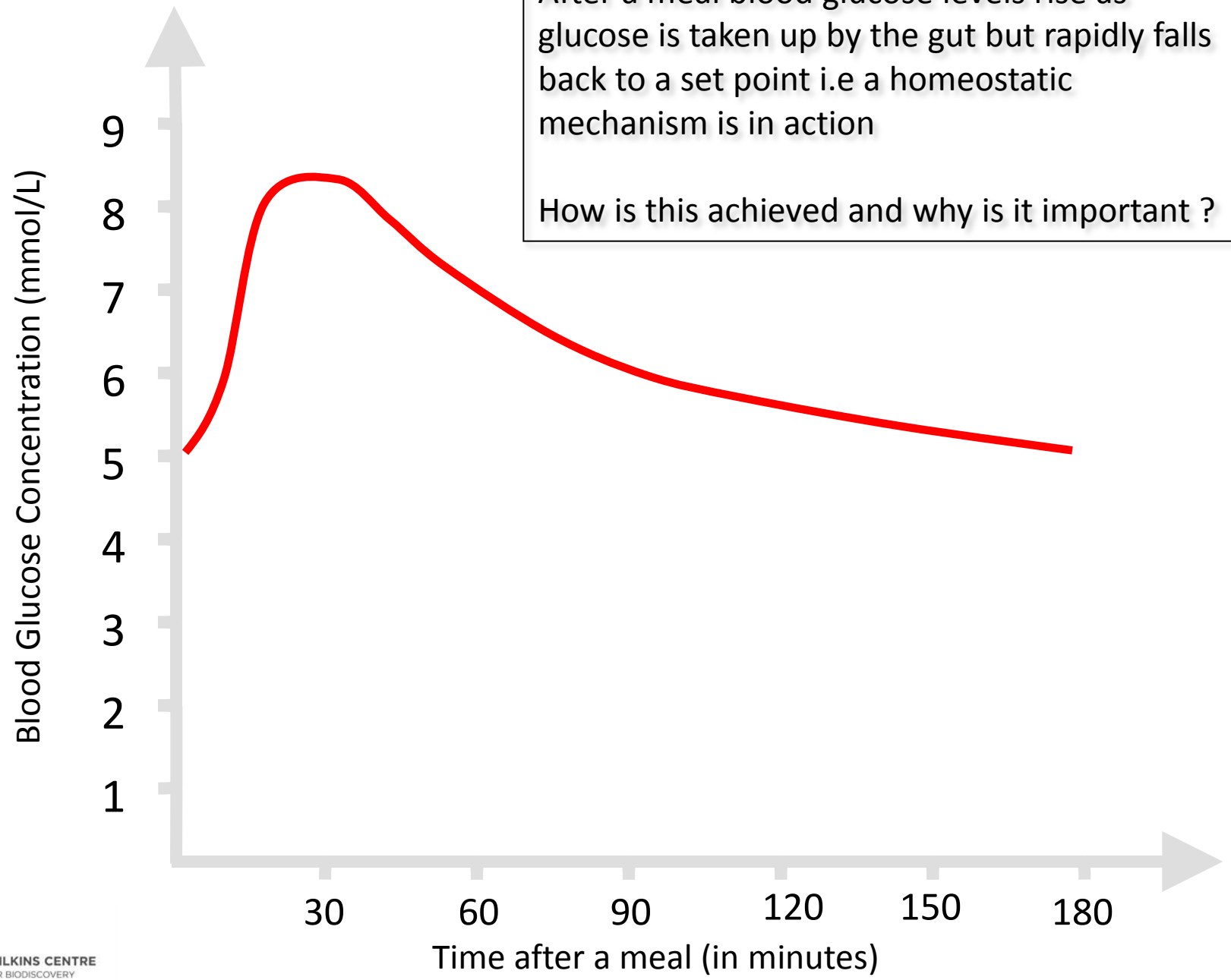
After a meal blood glucose levels rise as glucose is taken up by the gut but rapidly falls back to a set point i.e a homeostatic mechanism is in action

How is this achieved and why is it important ?



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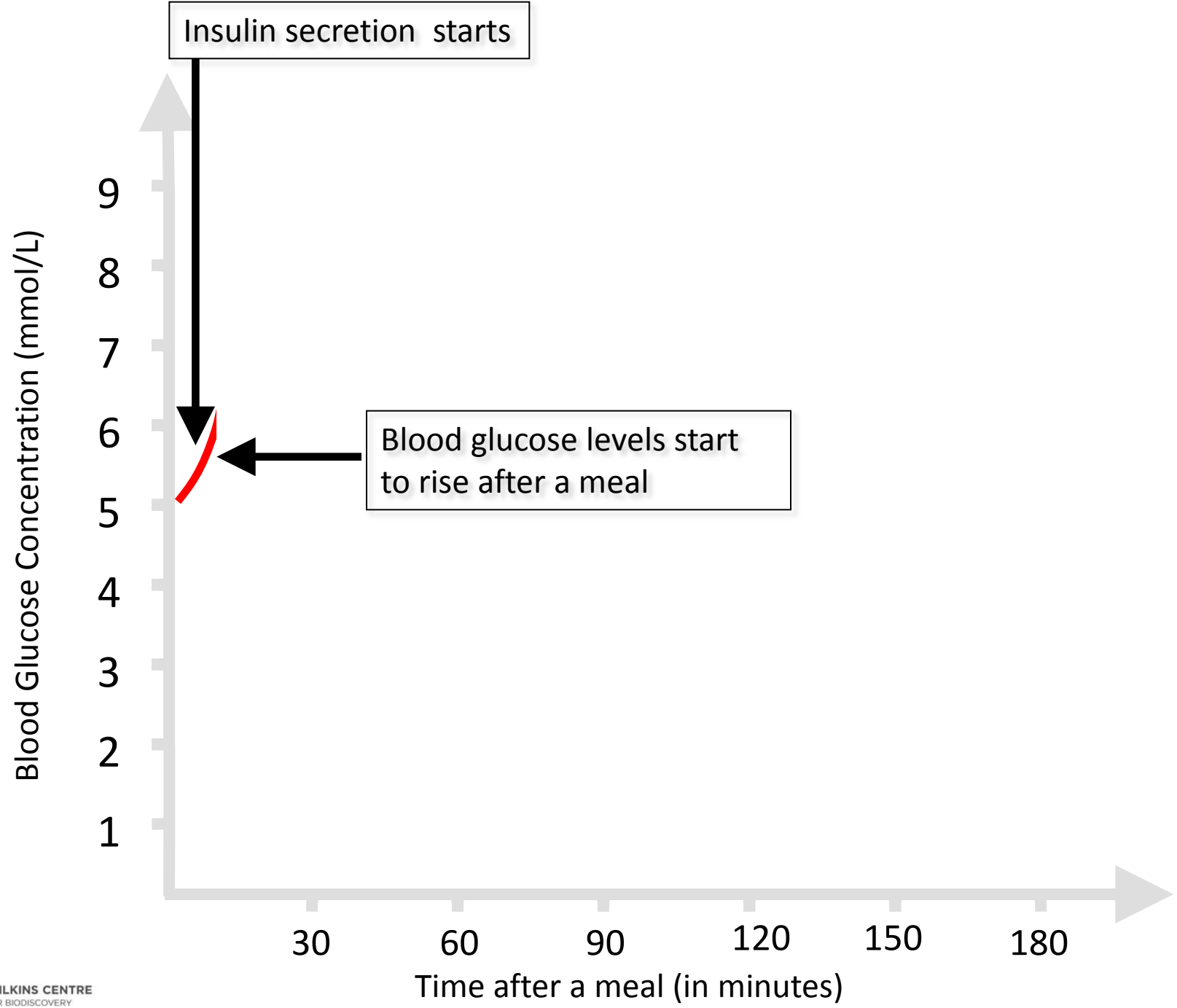

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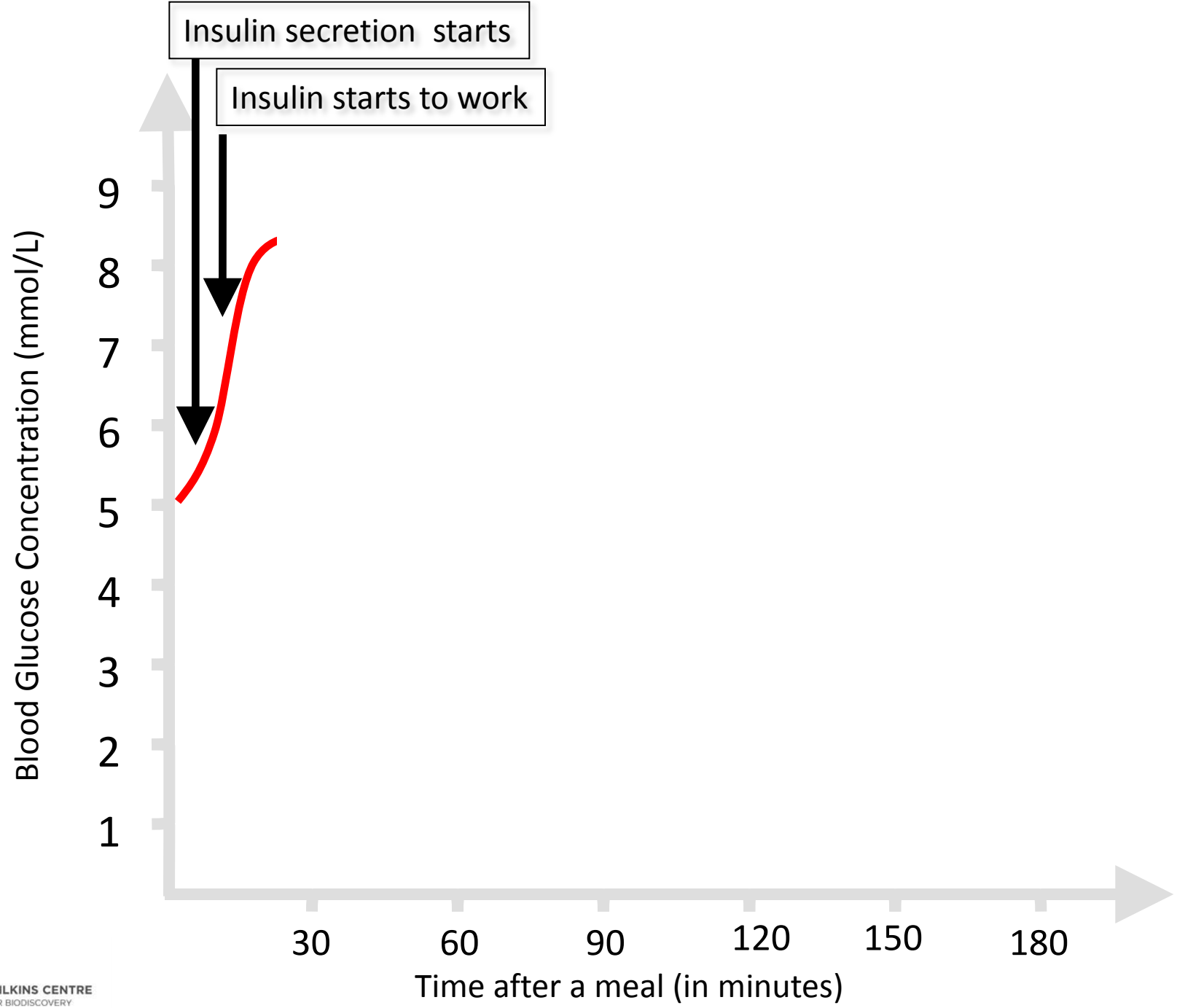

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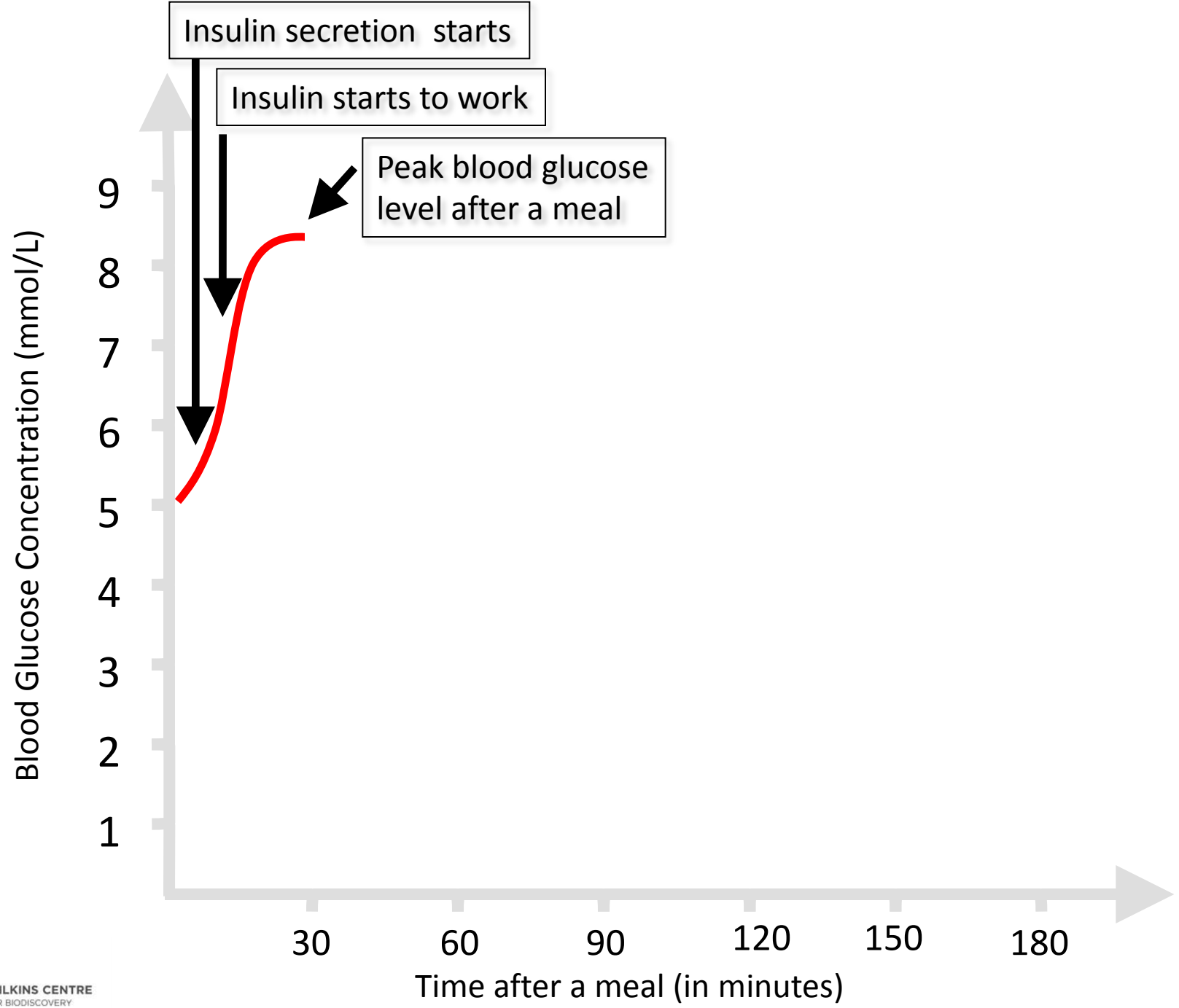

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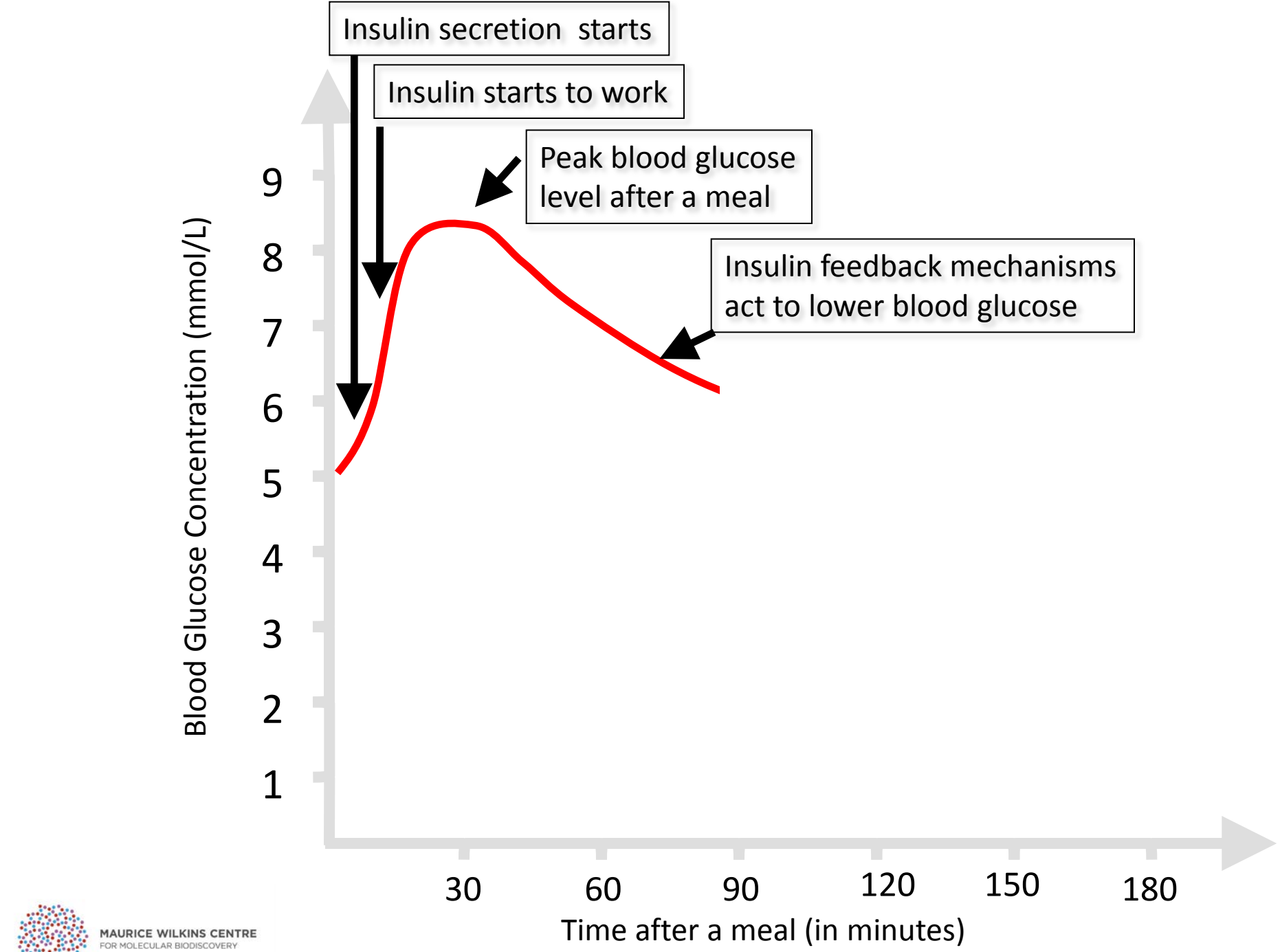

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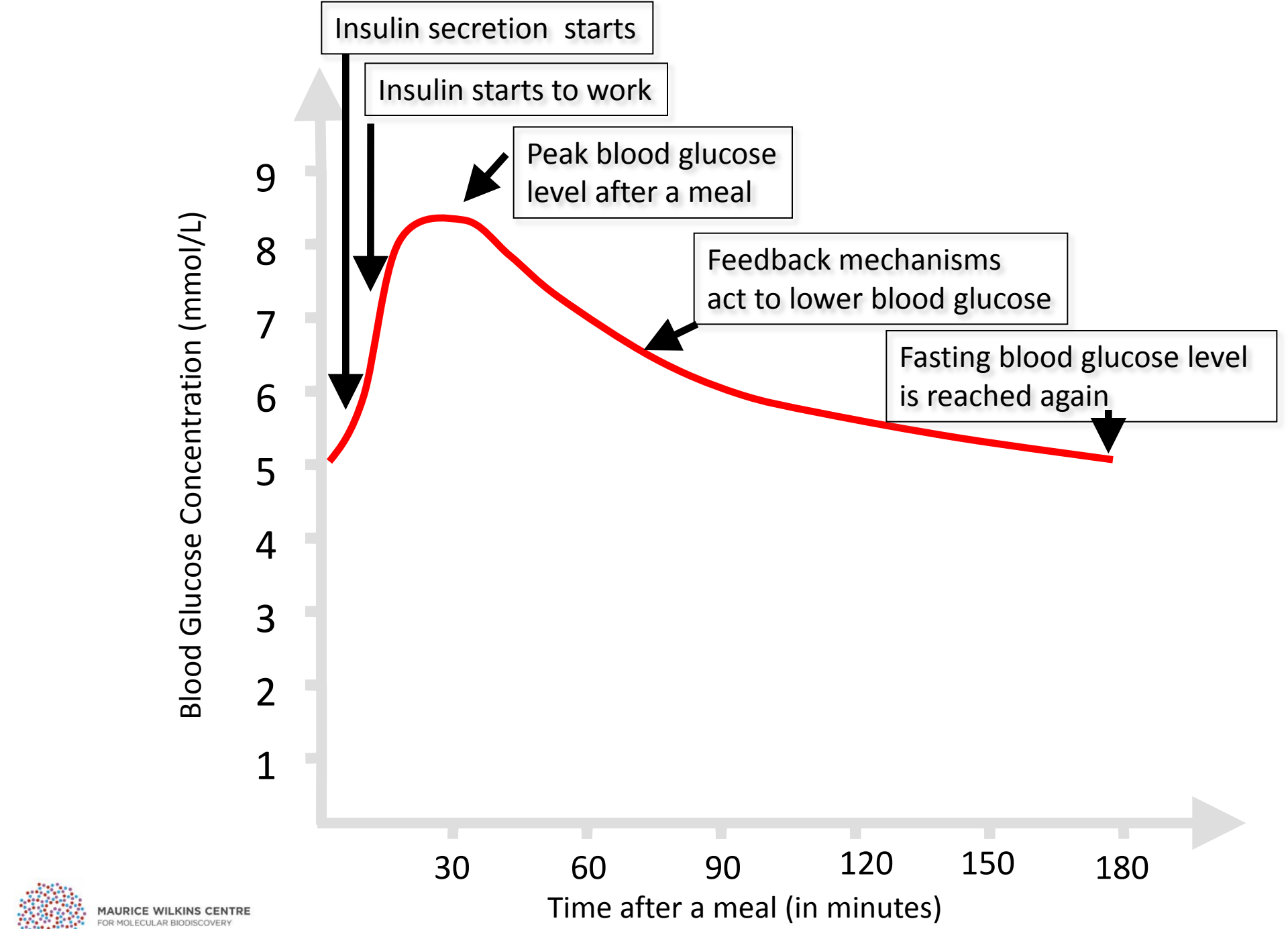

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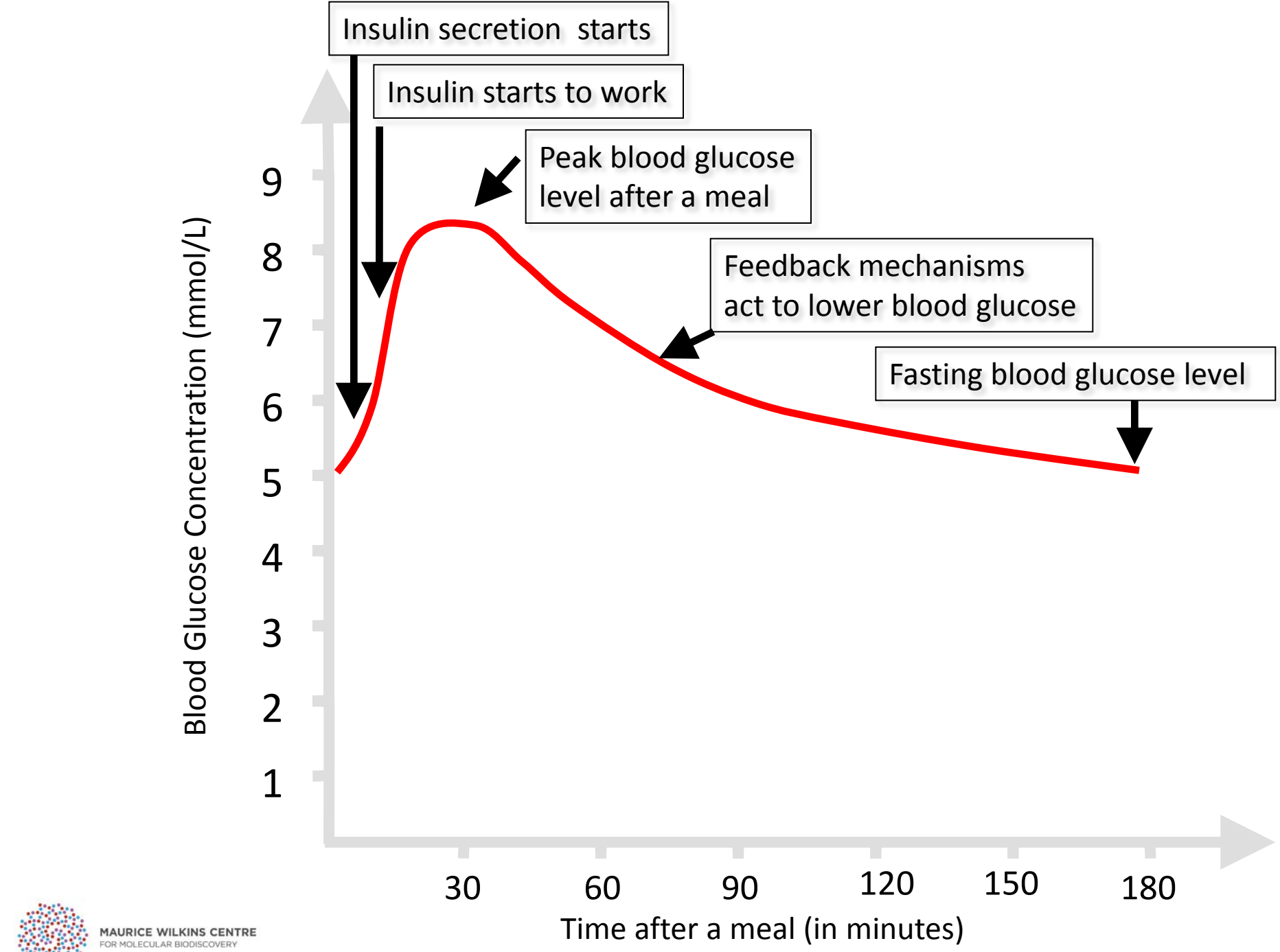

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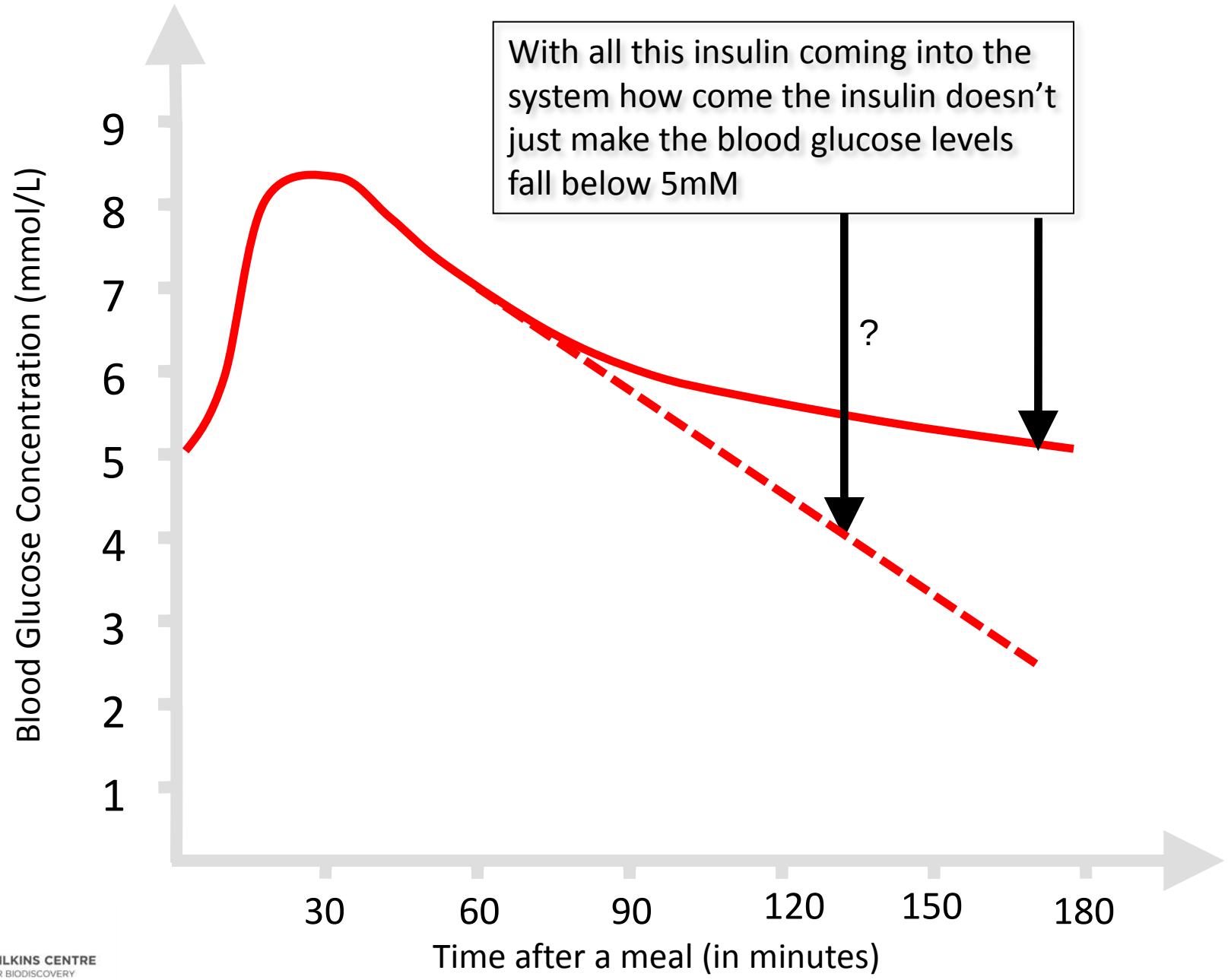

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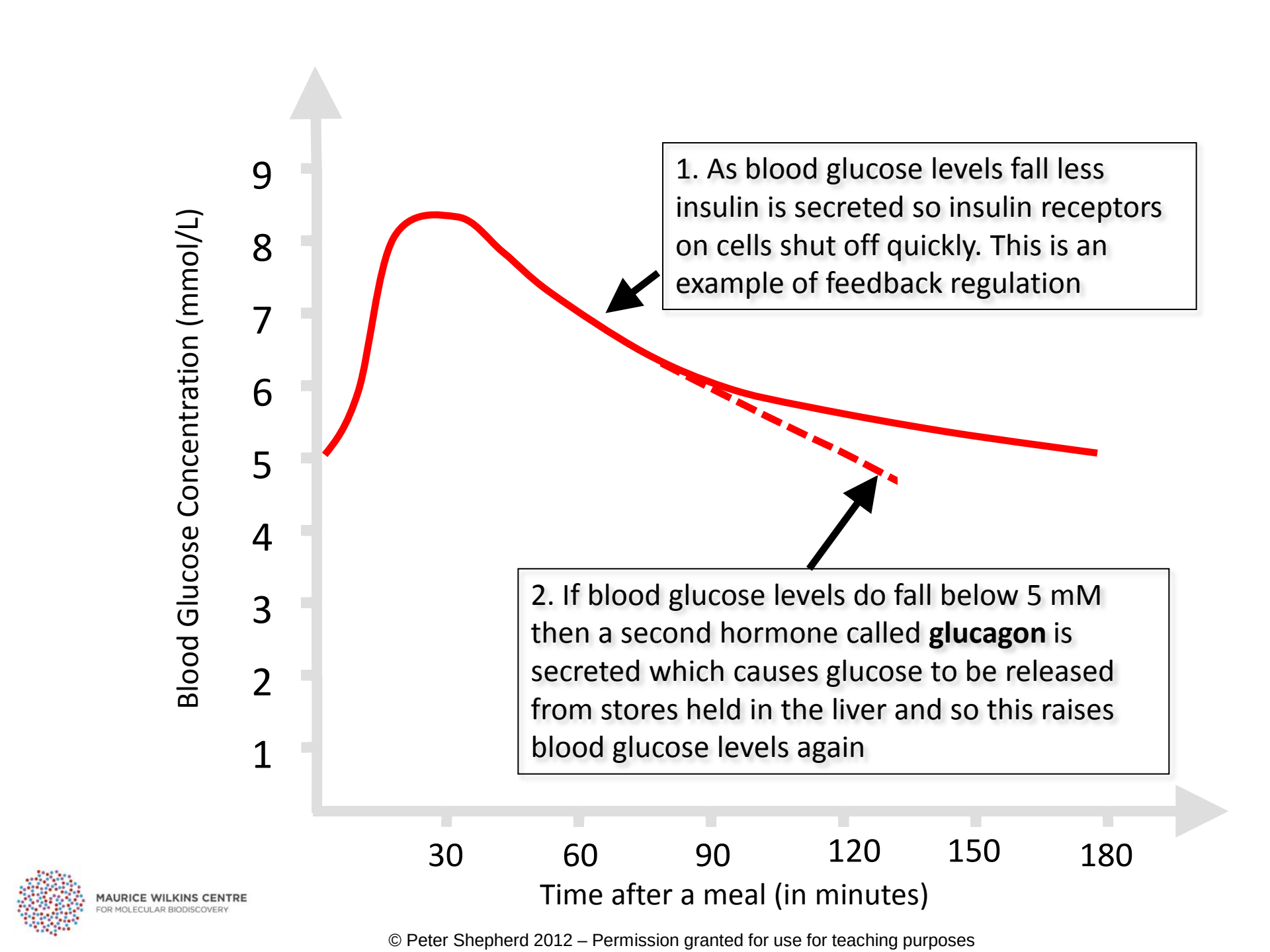

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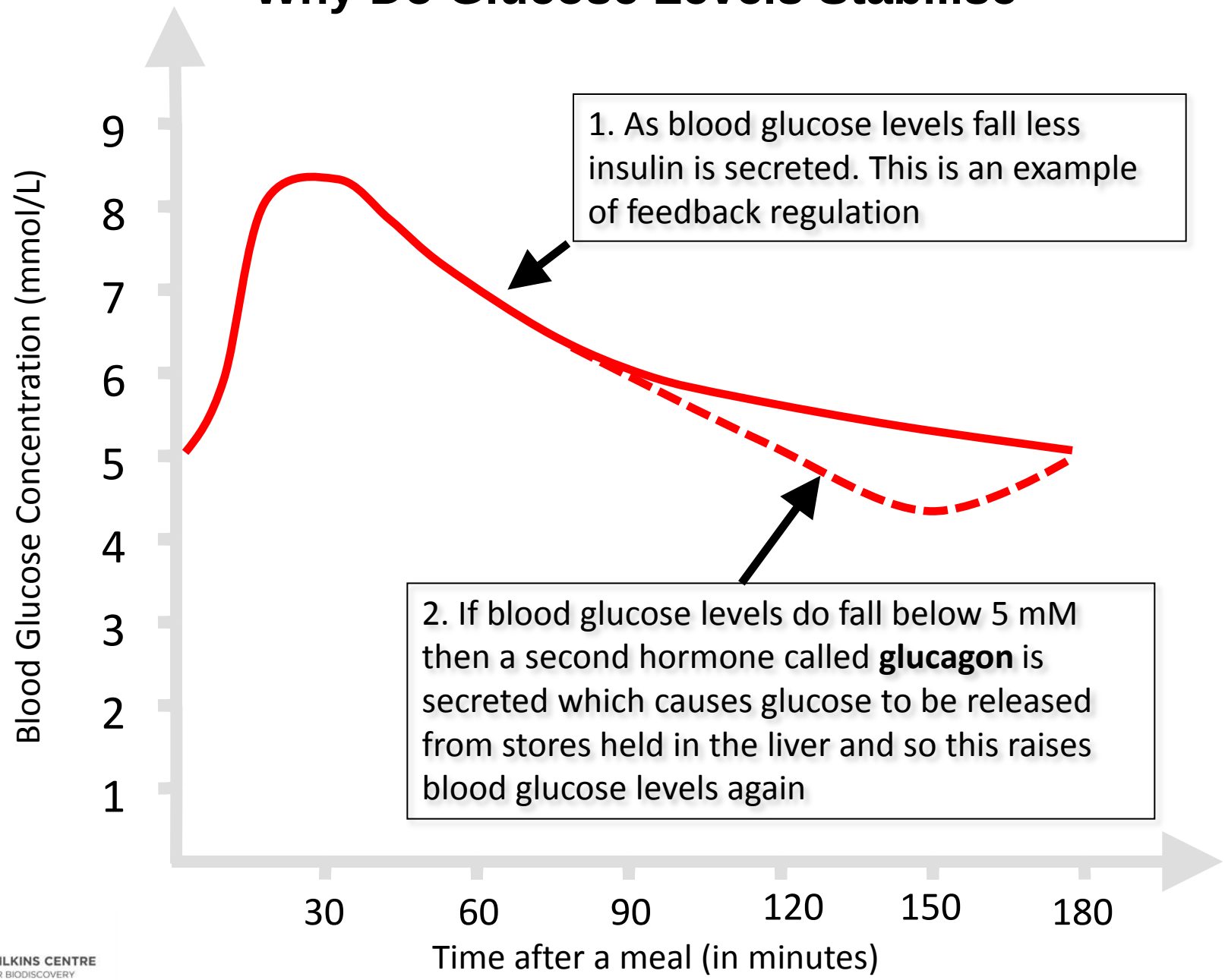
Why Do Glucose Levels Stabilise



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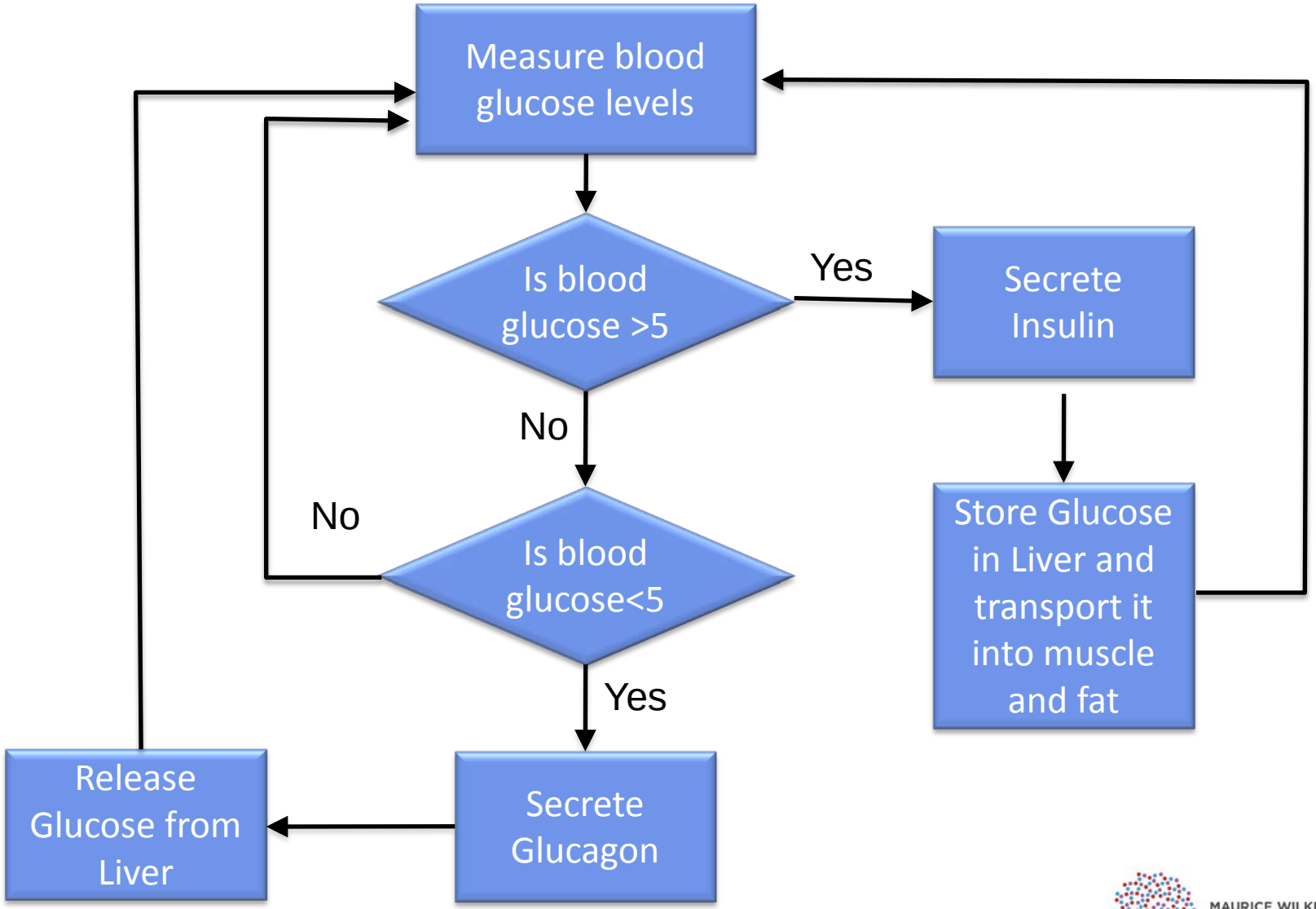
A computer programmers view of glucose homeostasis



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Insulin and Glucagon are Peptide Hormones

What is a hormone ?

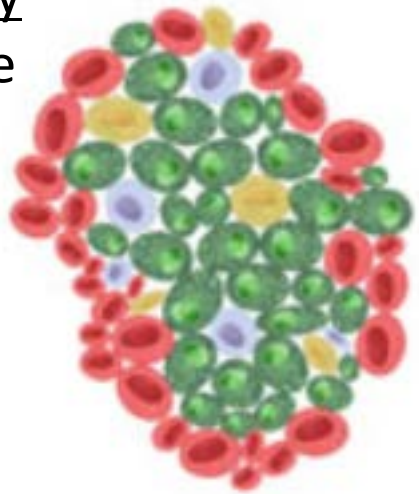
- Hormones are substances that are made in one part of the body to regulate processes in another part of the body.
- As such they are commonly used in feedback homeostatic mechanisms.
- Hormones are made at very low levels but can achieve very large effects in the body e.g. the concentration of insulin in the blood is usually in the picomolar range but it is able to achieve changes in glucose levels in the millimolar range.
- Each hormone has a very specific protein that it will bind to. These are called hormone receptors and once they are bound to the hormone they stimulate a particular response in the cell.
- Hormones circulate in the bloodstream until they find a cell that has the appropriate receptor on it
- Insulin receptors are mainly found in muscle, liver and fat
- Glucagon receptors are mainly in the liver

Some Examples of Hormones

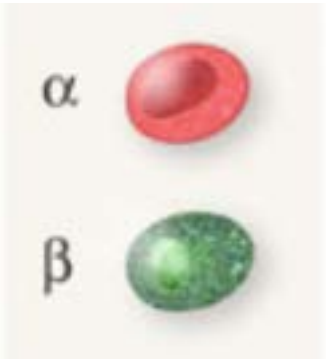
- Growth hormone – made in the pituitary gland and acts on growth hormone receptors found in many tissues in the body to promote growth
- Leptin – made in fat cells after a meal and acts on leptin receptors in an area of the brain called the hypothalamus. This leads to a response that reduces appetite and so reduces food intake.
- Steroid hormones – bind to steroid hormone receptors and increase growth of muscle. *Reputed to have been misused by some Belorussian shot putters to make them stronger*.
- Erythropoeitin – hormone that stimulates the production of new red blood cells. *Sometimes misused by Tour de France cyclists to boost their number of red blood cells.*

The Islets of Langerhans are the Central Regulator of Insulin and Glucagon Levels

- Insulin and glucagon are both hormones made only in a special group of cells in the pancreas called the Islets of Langerhans (or islets for short).
- The islets contain several cell types but the most important are
  - α-cells which sense when blood glucose falls below 5 mM and release glucagon
  - β-cells which sense when blood glucose rises above 5 mM and release insulin
- The pancreas is adjacent to the gut and on the portal vein which drains nutrients from gut to liver.
- This means islets are very well placed to sense an influx of nutrients and to respond by releasing hormones.



Islet cell structure



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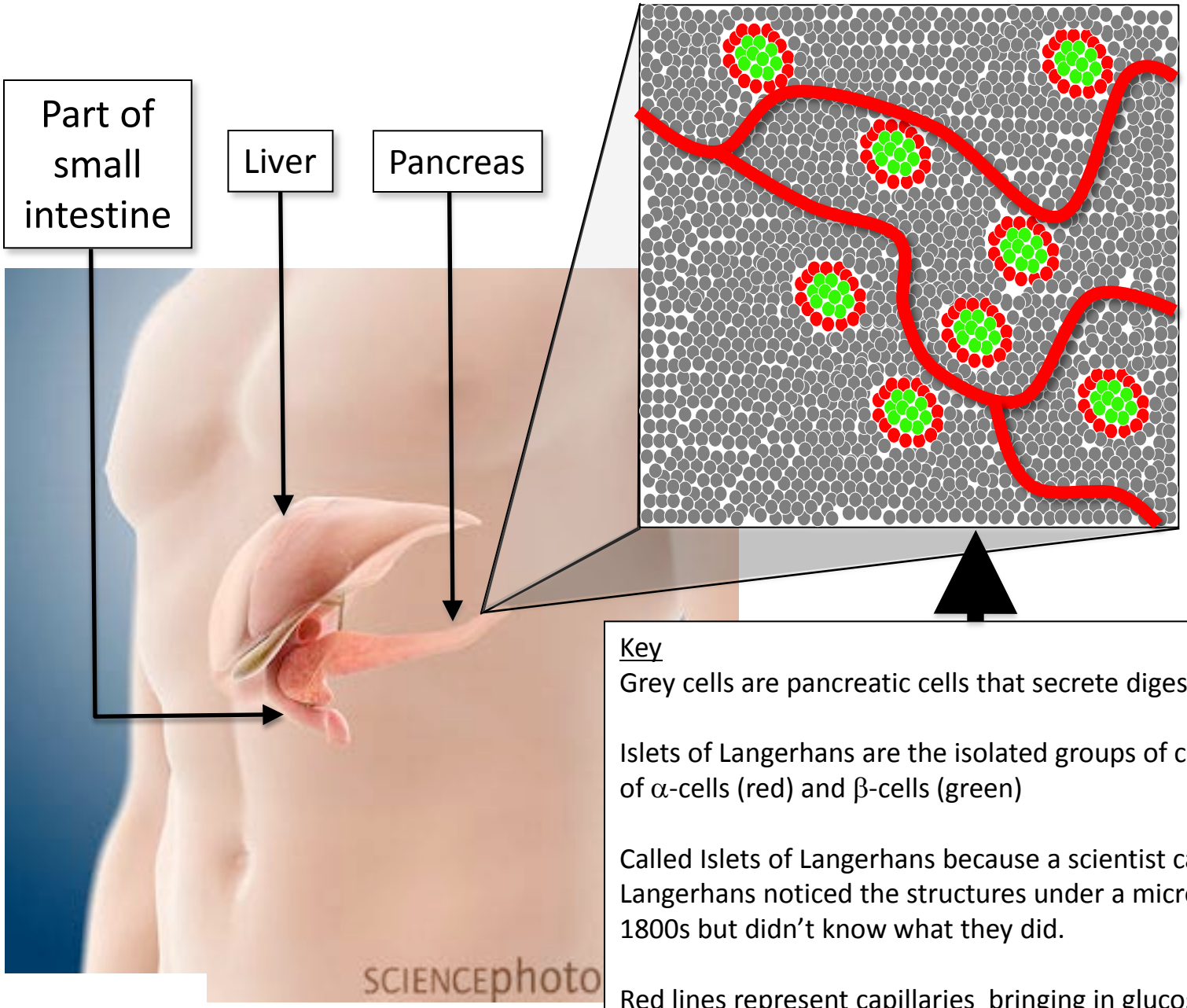


Key

Grey cells are pancreatic cells that secrete digestive enzymes

Islets of Langerhans are the isolated groups of cells made up of α-cells (red) and β-cells (green)

Called Islets of Langerhans because a scientist called Paul Langerhans noticed the structures under a microscope in 1800s but didn't know what they did.

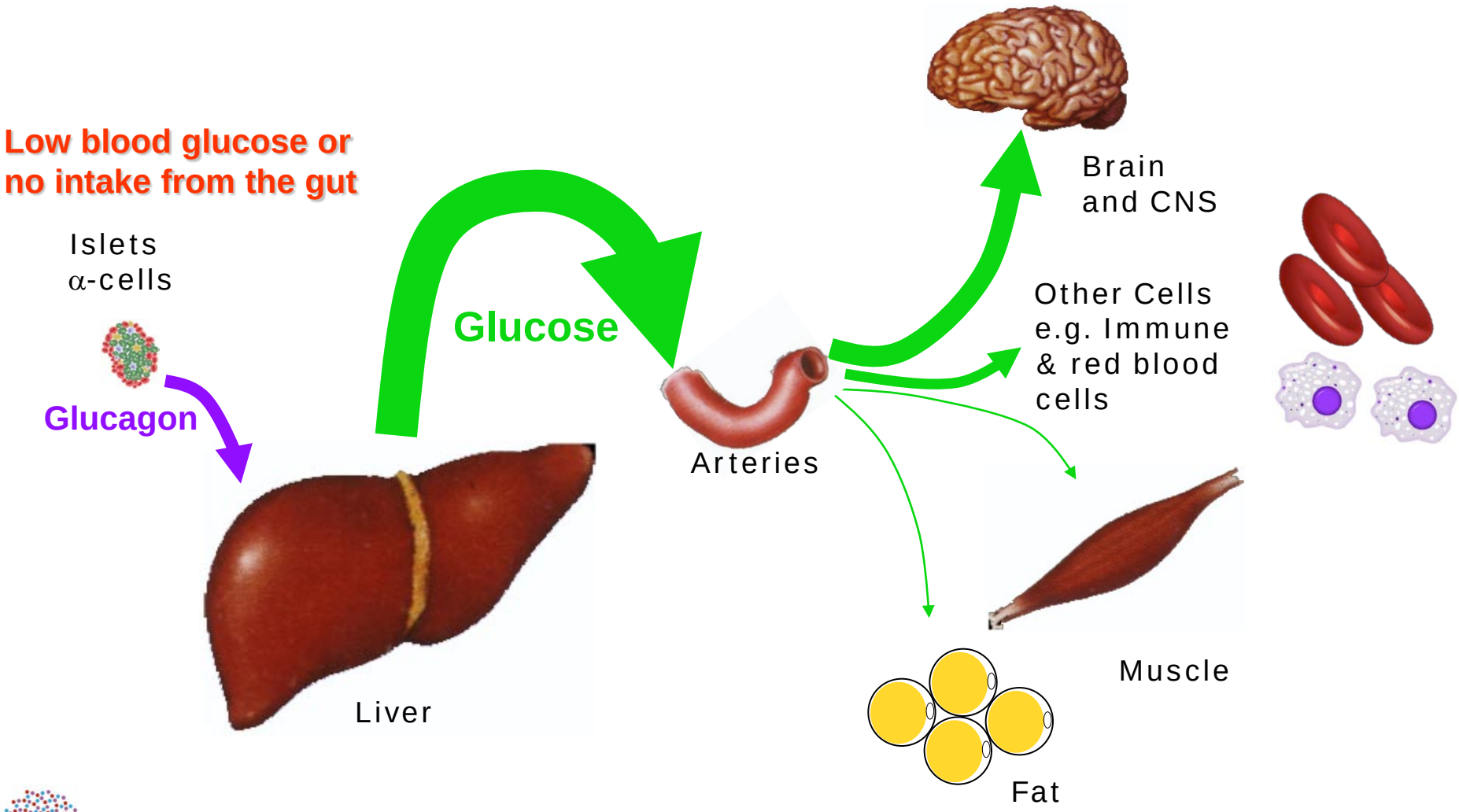
Red lines represent capillaries bringing in glucose and taking hormones away

From Life Process, Ecology and Evolution – Published by Pearson 2012

What Happens Between Meals

- Glucose levels fall and glucagon is released
- Glucagon binds to receptors that are found on cells in the liver
- This stimulates the release of glucose from the liver where it has been stored as long polymeric chains of glucose called glycogen

Where Glucose Comes From Between Meals



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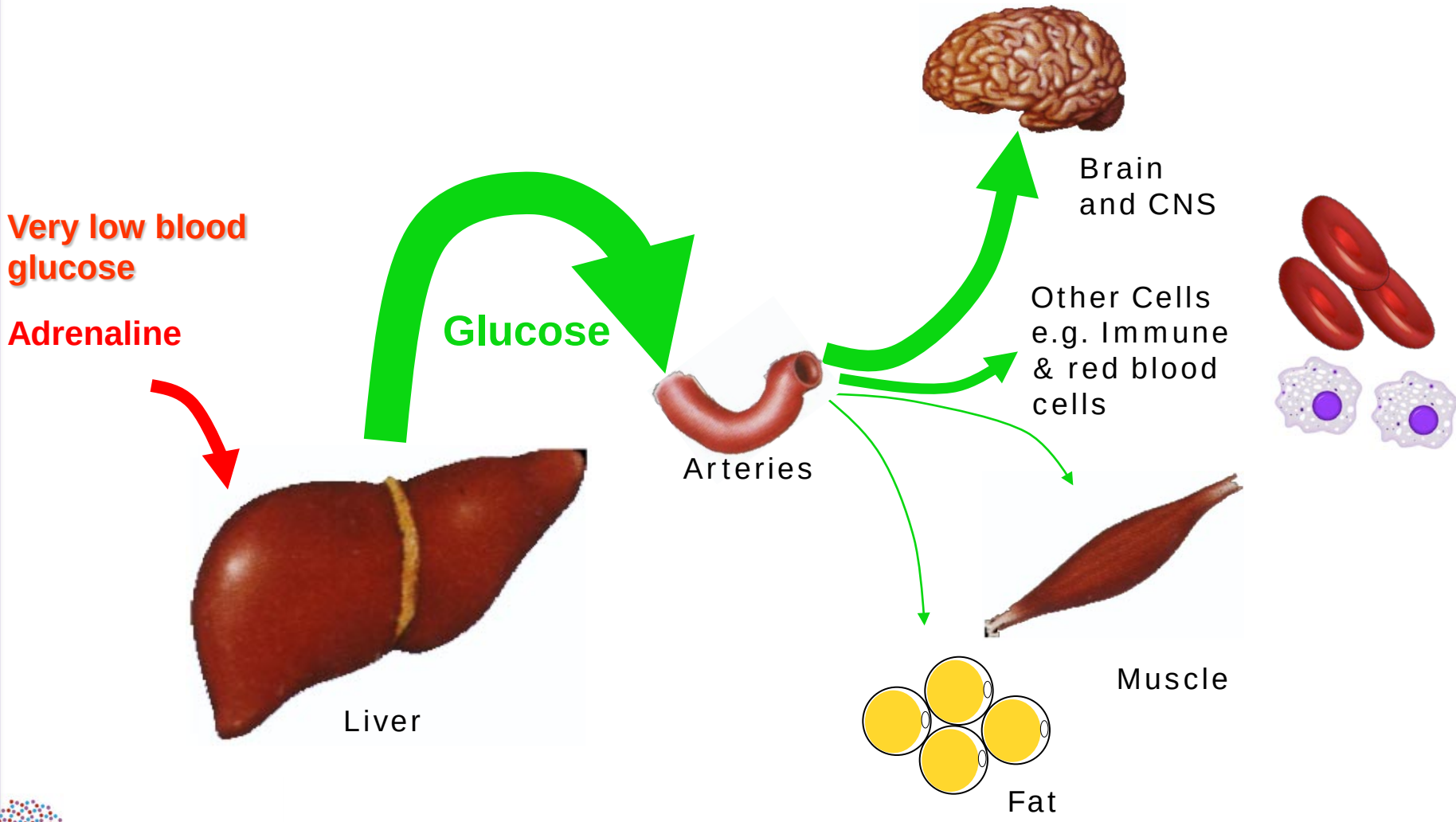
If an Emergency occurs that Requires Lots of Glucose then an "Emergency Glucose Resuscitation System" Kicks In



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What Happens if Glucose Levels Get To Low

Because the brain and blood cells need glucose the body has developed emergency measures when blood glucose get dangerously low (known as a “hypo”) as might happen if a Type-1 diabetic administers to much insulin.

•Symptoms appear (called “hypoglycemic awareness”) including fatigue, irritability, nervousness, depression, flushing, memory loss, loss of concentration, headaches, dizziness, fainting, blurring of vision, ringing in the ears, numbness, tremors, sweating and heart palpitations.

•These are stimulated by signals from the brain that is sensing the low glucose and part of this response is to increase adrenaline levels in an attempt to increase blood glucose levels.

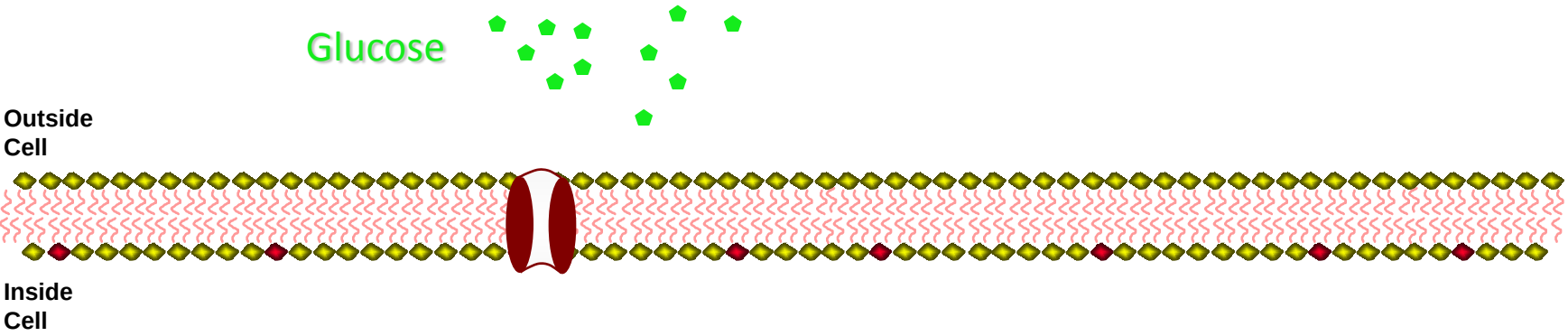
•The warning signs are very useful for a Type-1 diabetic as the hypoglycemia can easily be overcome by taking in some glucose.

•Unfortunately the ability to detect hypoglycemia sometimes get lost by diabetics (a condition termed “hypoglycemic unawareness”).

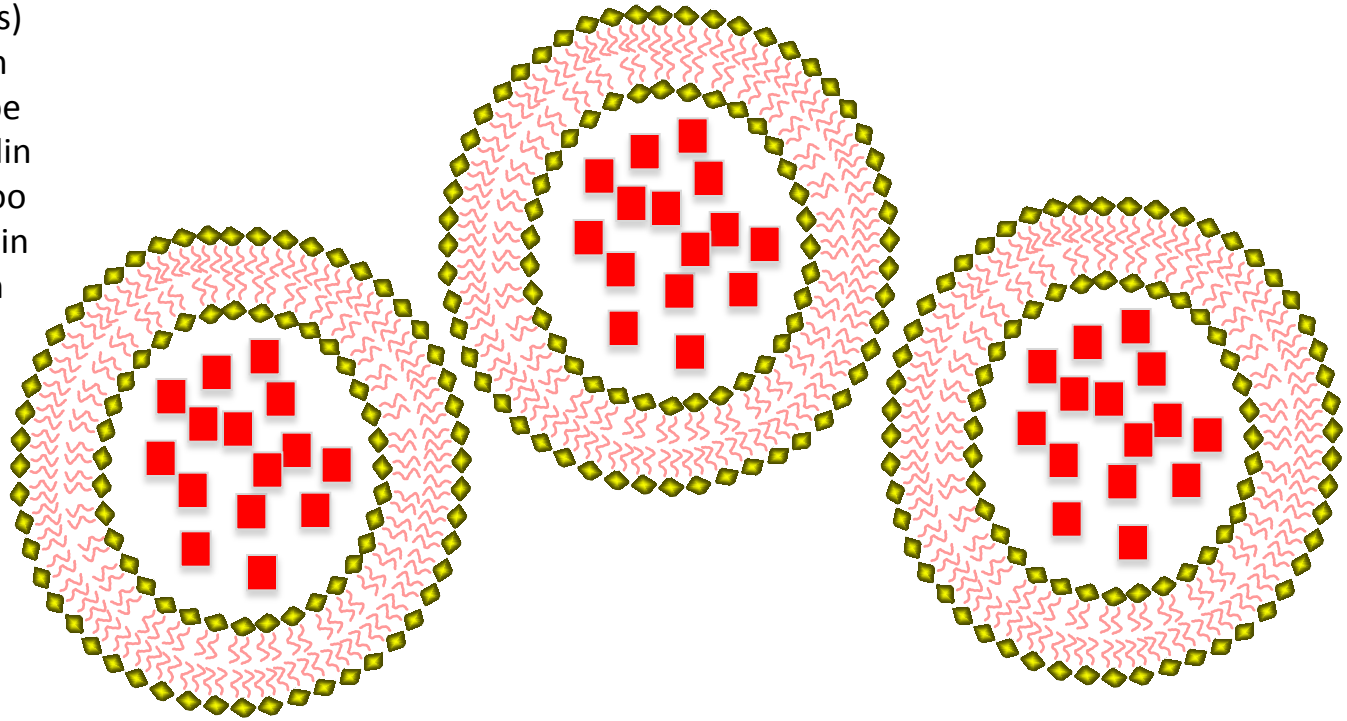
What Happens After a Meal

- Glucose levels rise and insulin is released
- Insulin binds to receptors that are found on cells in the liver, in muscle and in fat cells
- This stimulates the uptake of glucose into these tissues so blood glucose levels go down
- Glucose taken up by liver is mostly stored as glycogen
- Some of the glucose going into fat cells contribute to the accumulation of fat in these cells

How is Insulin Released from β-cells



We need to release insulin very quickly (within a few minutes) but it takes 30 minutes to an hour for the insulin gene to be switched on and for new insulin protein to be made. This is too slow so the β-cells make insulin in advance and package it in vesicles just waiting for the increase in glucose levels to occur.



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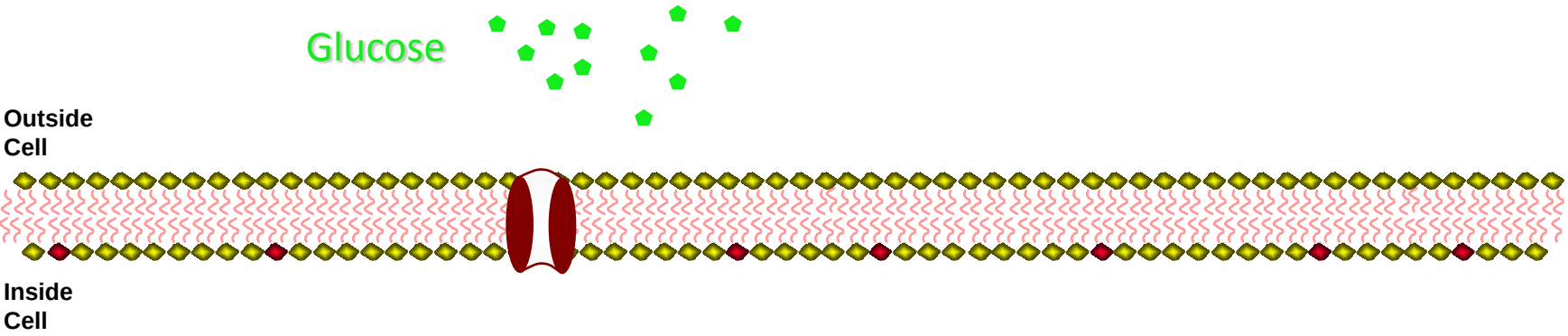
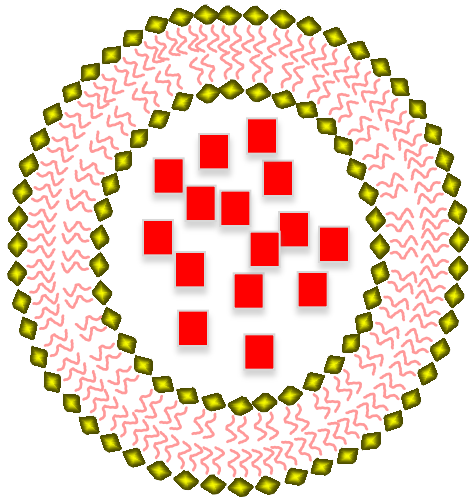
How is Insulin Released from β-cells



The extra glucose coming into the β-cell triggers the insulin containing vesicle to move the the plasma membrane and to fuse with the plasma membrane , so releasing the contents (i.e the insulin) to the bloodstream



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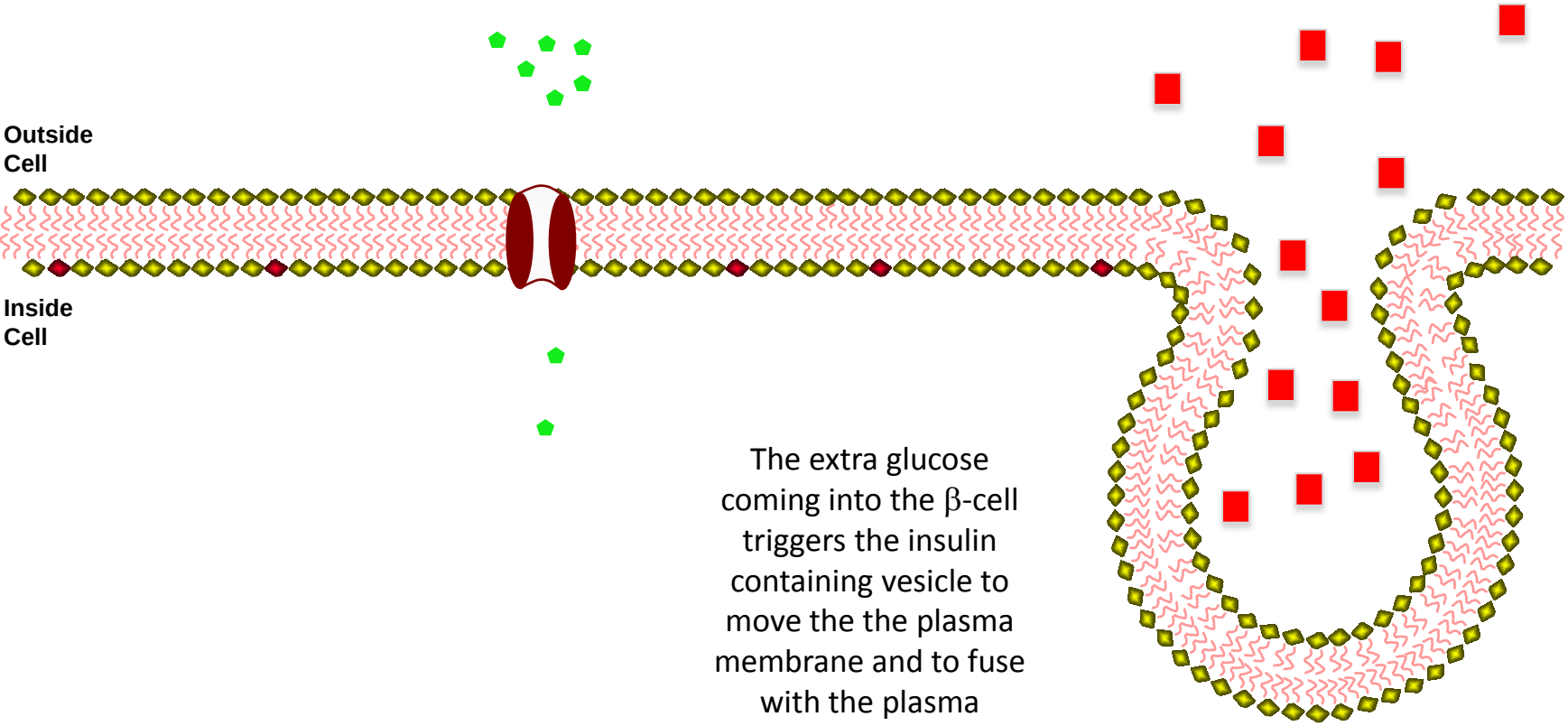
How is Insulin Released from β-cells



The extra glucose coming into the β-cell triggers the insulin containing vesicle to move the the plasma membrane and to fuse with the plasma membrane , so releasing the contents (i.e the insulin) to the bloodstream

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What Happens When Insulin Binds to its Receptor

- Insulin moves through the blood stream until it finds its specific receptor on the surface of the liver cells, muscle cells and fat cells.
- The receptor is a protein that spans the membrane
- The binding of insulin causes an allosterically induced change in the shape of the intracellular portion of the receptor which activates an enzymatic activity.
- The receptor is now said to be activated and as shown in later slides this brings about changes inside the cell.
- This is in effect allowing the hormone on the outside of the cell to regulate functions inside the cell even though the hormone has not entered the cell. This is called “transduction” and the whole process is often called signal transduction.

How Does Insulin Work and How is the Signal Shut Off

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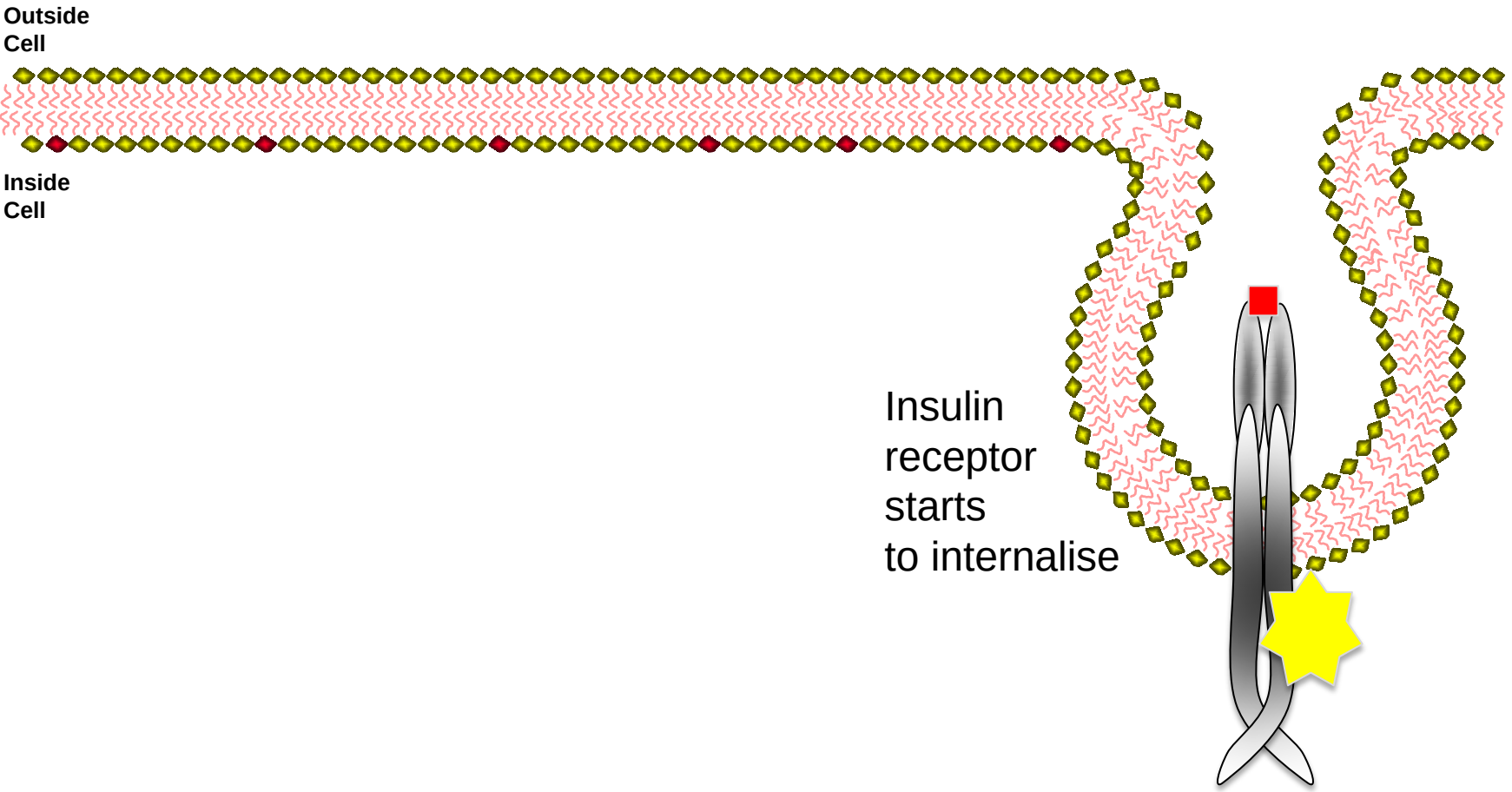
What Happens When Insulin Binds to its Receptor

- As soon as this receptor is activated, a second thing also happens. That is that the the membrane around the receptor starts to invaginate.
- Eventually this completely pinches off so the insulin receptor is now inside a vesicle.
- The vesicle next gets acidified and as you know from Year 12 protein structure is changed by acids. In this case it means that insulin can no longer bind to its receptor so the signal is shut off.
- The insulin then gets chopped up by an enzyme called insulin degrading enzyme which is a type of enzyme called a protease i.e one that chops up proteins.
- This all happens in around a minute so it means that if insulin is to continue to be effective in muscle, liver and fat then new insulin must arrive at the cell and that soon after insulin levels start to fall that insulin's actions in the cell will also cease.

How Does Insulin Work and How is the Signal Shut Off



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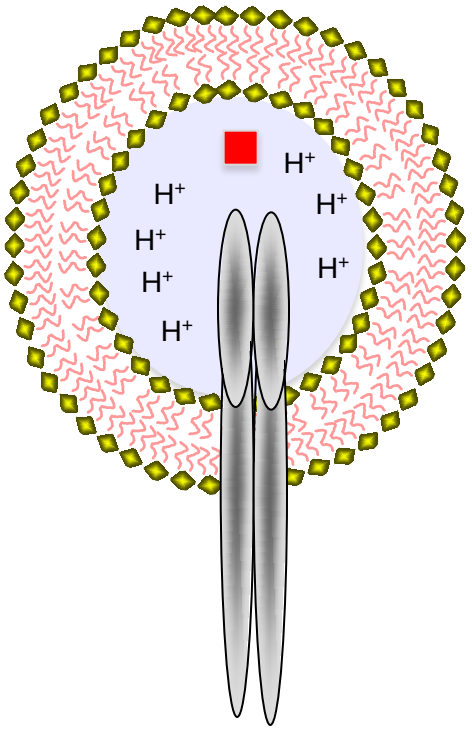
How Does Insulin Work and How is the Signal Shut Off

Outside Cell

Inside Cell

Insulin signal shut off



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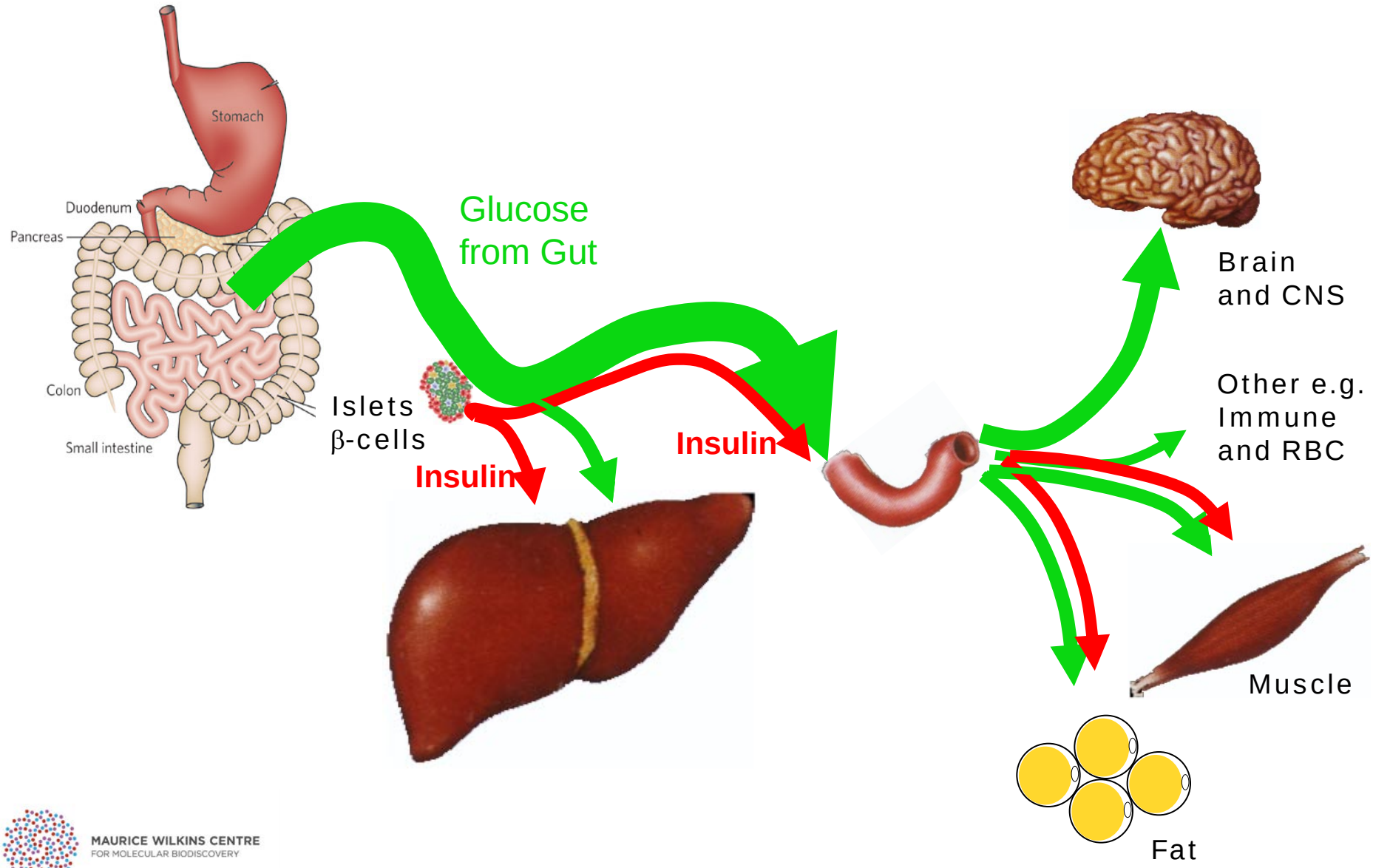
Many other hormones work in a broadly similar way so if you understand how insulin works then its quite easy to understand how other hormones work.

What Happens to Glucose After A Meal



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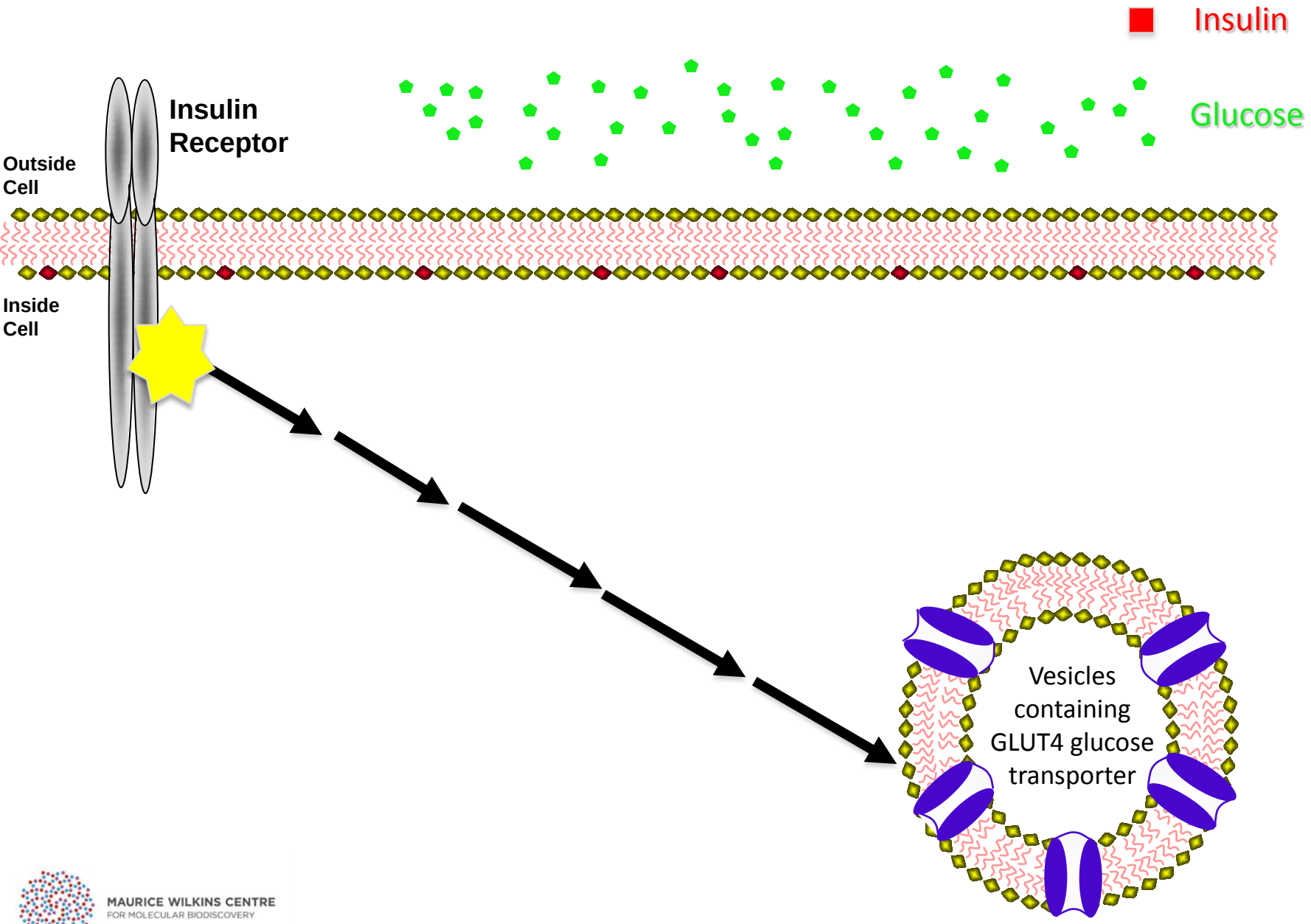
How Does Insulin Stimulate Glucose Uptake Into Muscle and Fat

•Glucose transport in muscle and fat is different from other tissues as muscle and fat have a glucose transporter called GLUT4 that can do this but when insulin is absent the GLUT4 is inside the cell so cannot transport glucose

•When insulin binds to the insulin receptor on the cell surface it allosterically causes a shape change in the intracellular part of the molecule which activates an enzymatic activity in the intracellular portion of the receptor. Thus a signal is transmitted from the extracellular environment to the intracellular one without the hormone having to enter the cell.

•The insulin receptor can now add phosphates onto certain proteins inside the cells to start a chain reaction of enzymes inside the cell that ultimately makes the vesicles containing the GLUT4 move to the plasma membrane. These vesicles fuse with the plasma membrane so the GLUT4 is now in the plasma membrane where it can now transport glucose into the muscle and fat cells

How Does insulin Stimulate Glucose Uptake Into Muscle And Fat



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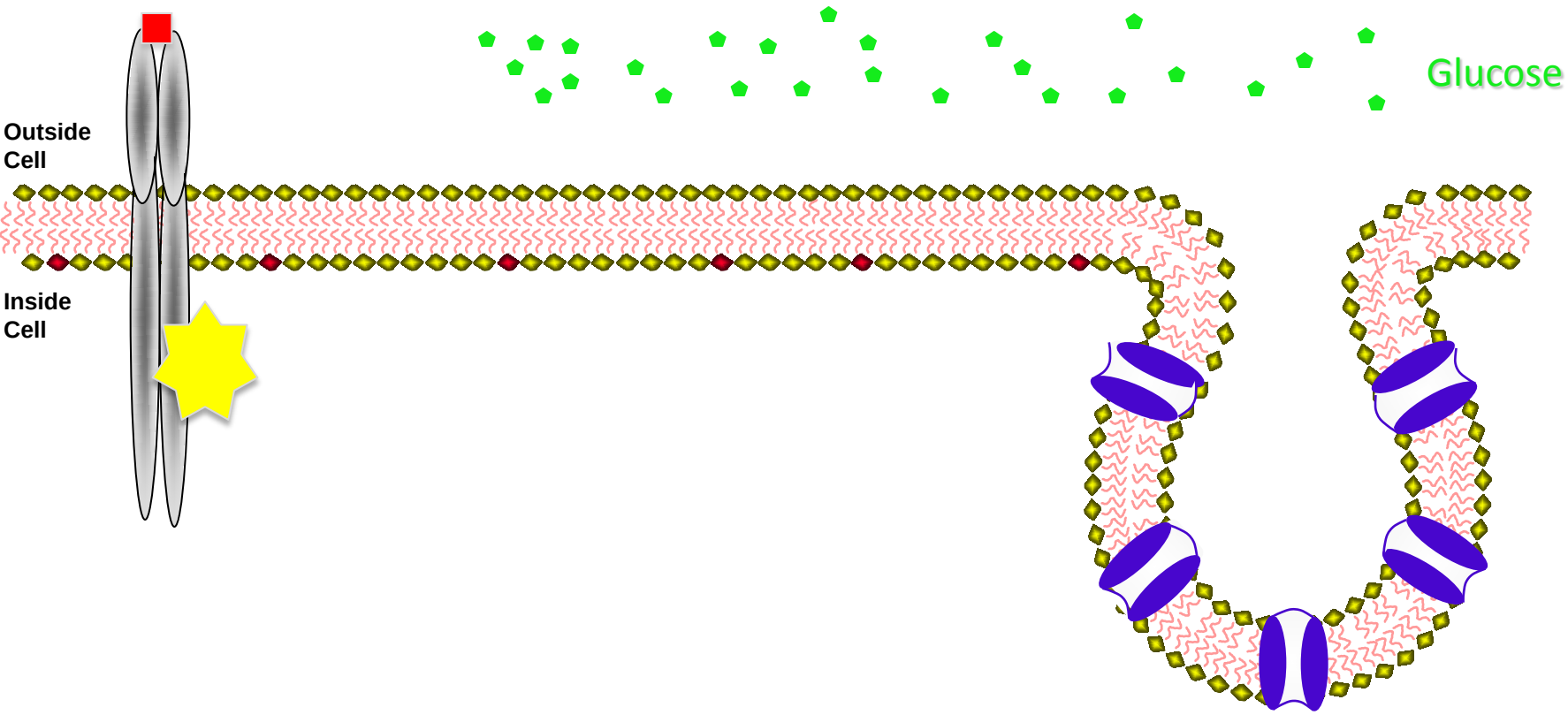
How Does insulin Stimulate Glucose Uptake Into Muscle And Fat



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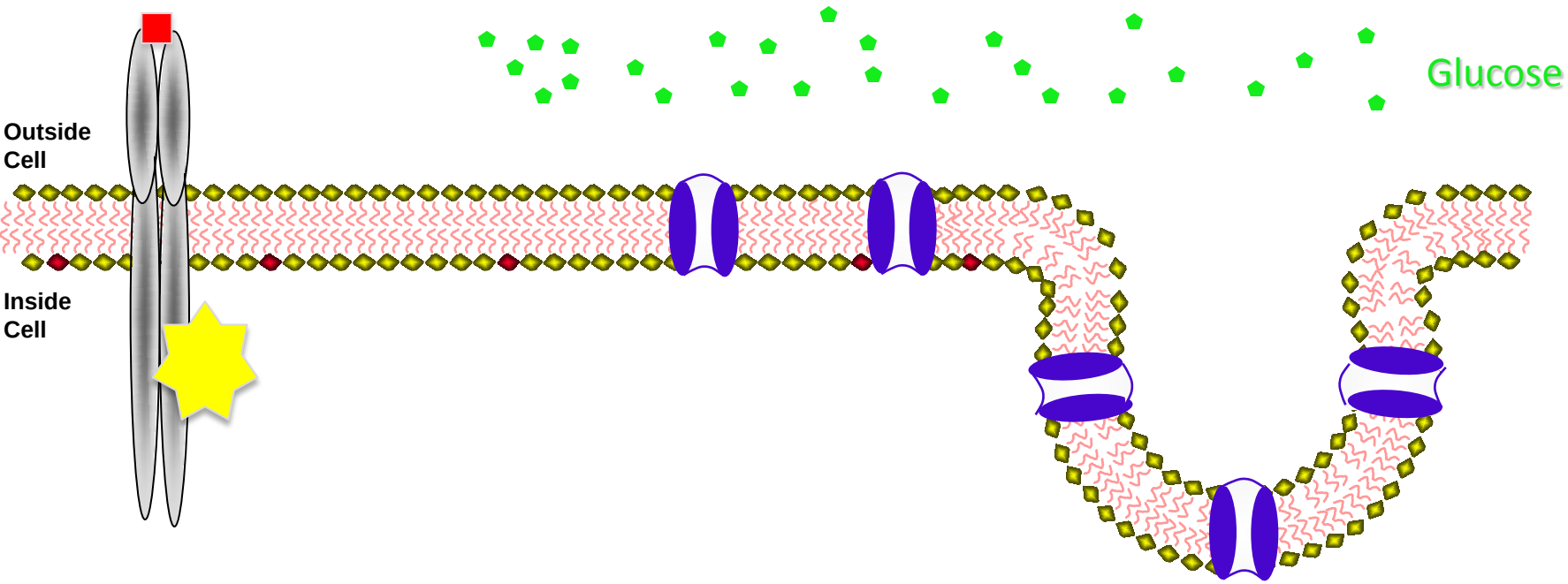

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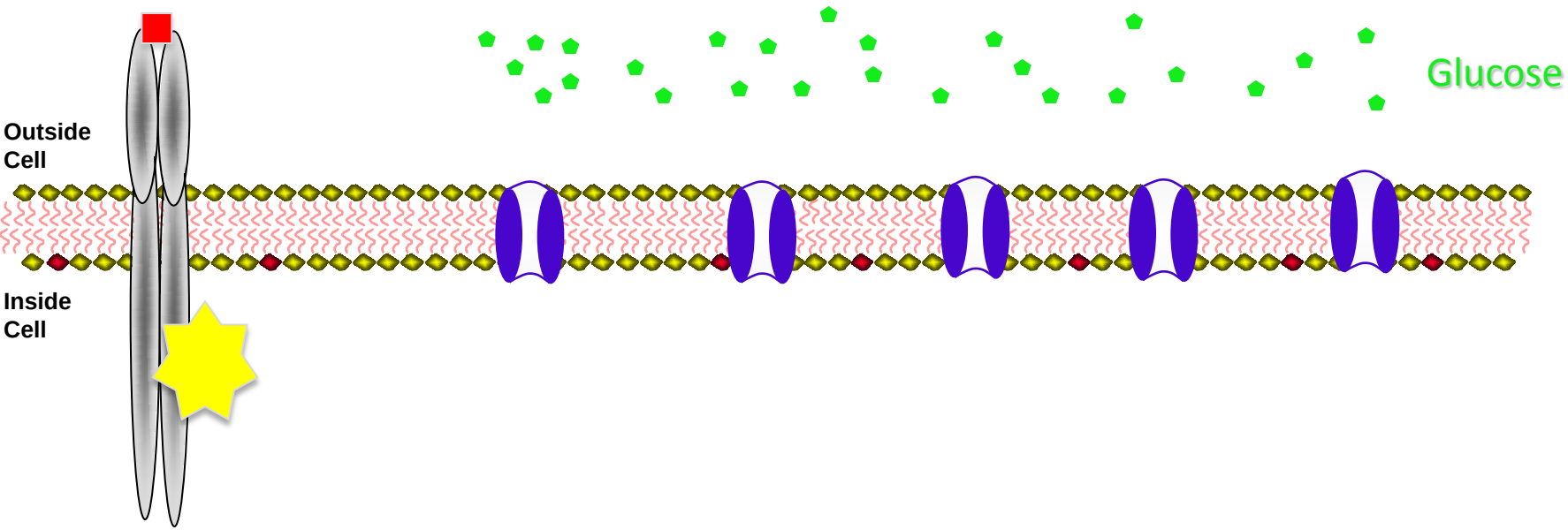
How Does insulin Stimulate Glucose Uptake Into Muscle And Fat



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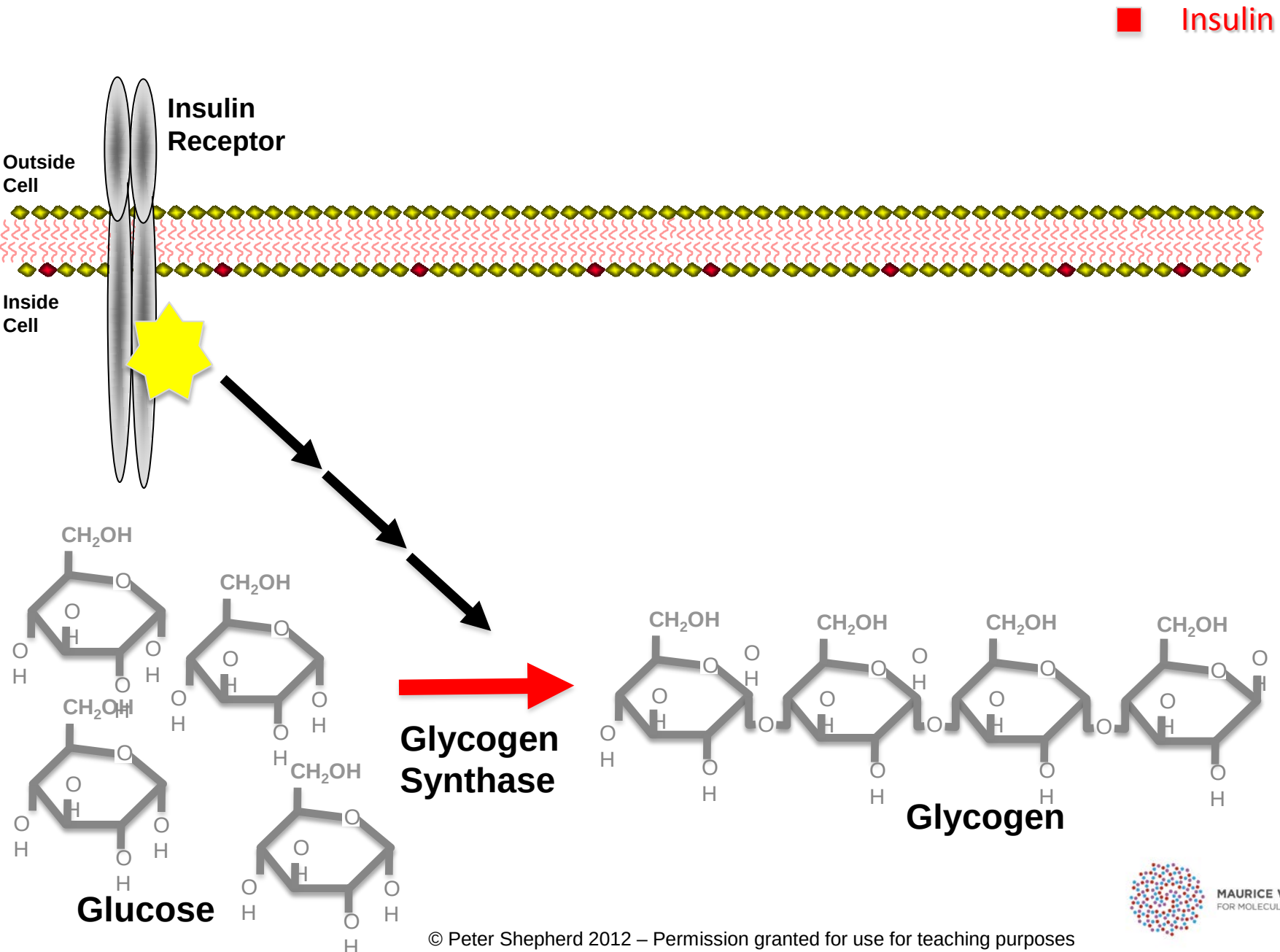
How Do Insulin and Glucagon Regulate Glycogen Levels in Liver

- Insulin binds to its receptor on the surface of liver cells and activates signaling pathways that result in the activation of an enzyme called glycogen synthase which catalyses the formation of glycogen polymers

- Glucagon binds to its receptor on the surface of liver cells and activates signaling pathways that result in the activation of an enzyme called glycogen phosphorylase which catalyses the breakdown of glycogen polymers back into glucose

How Does insulin Stimulate Glycogen Synthesis in Liver



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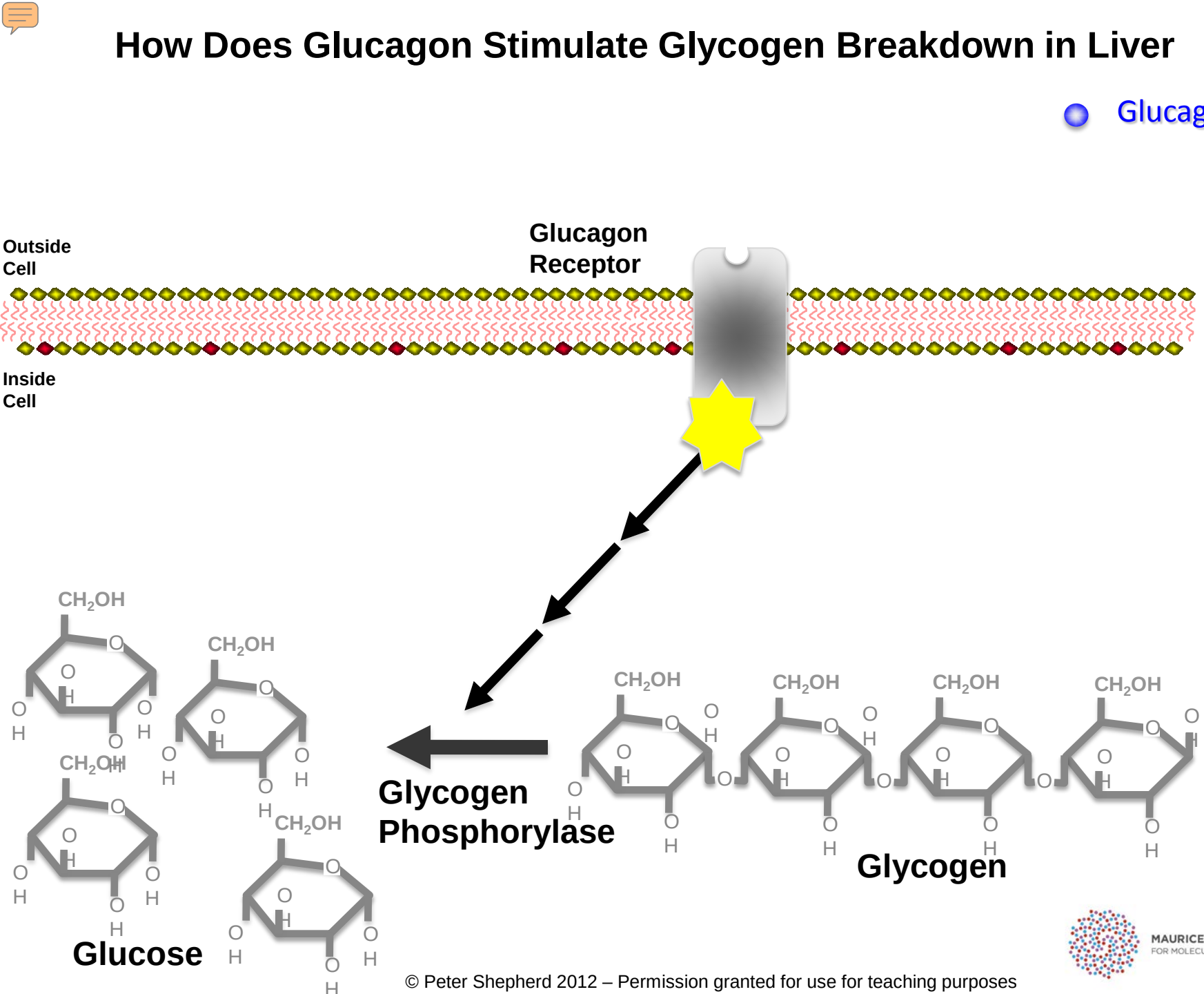
How Does Glucagon Stimulate Glycogen Breakdown in Liver



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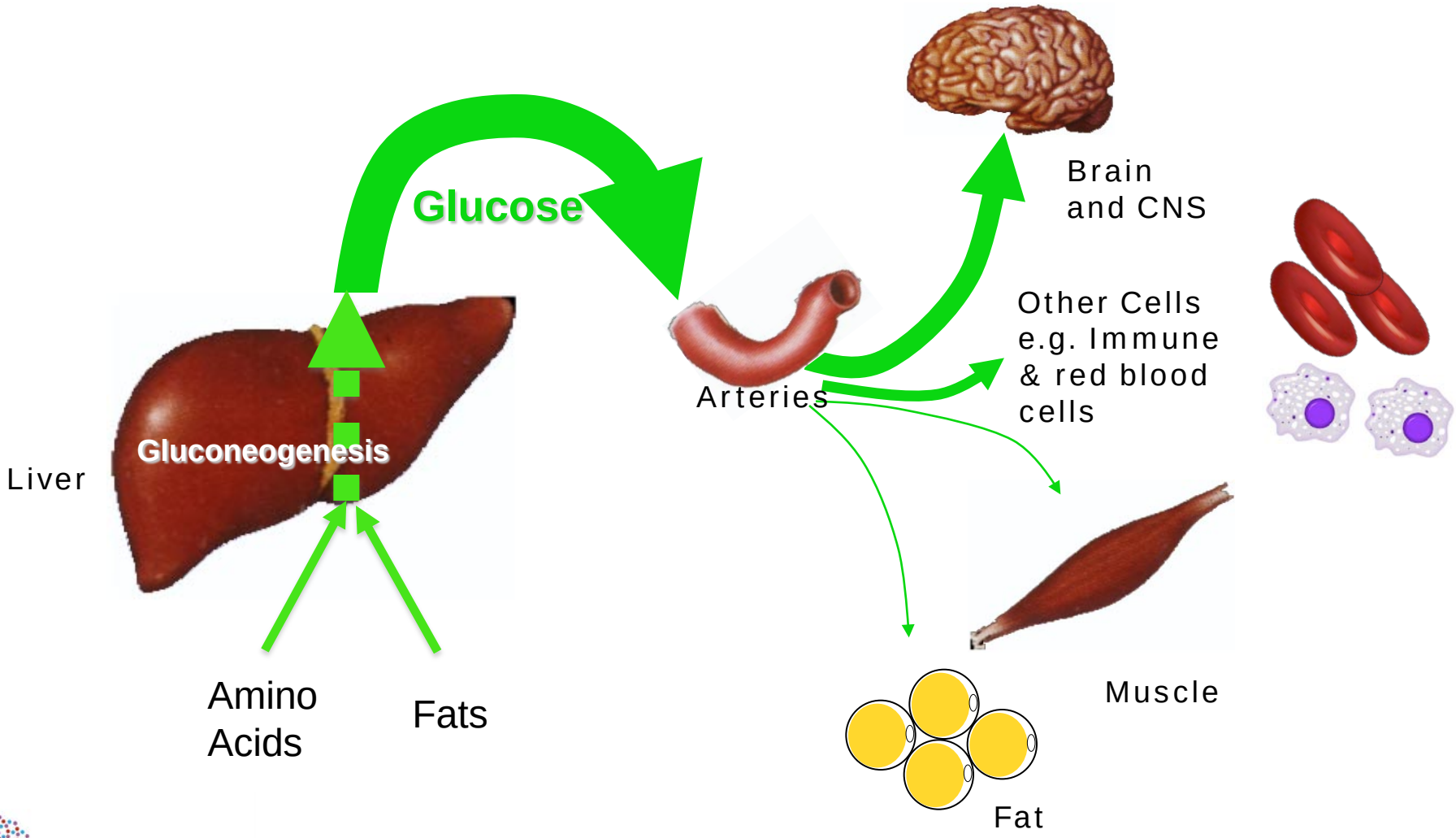
What Happens During Prolonged Starvation

- After 2-3 days without food the stores of glycogen in the liver become depleted but the liver can adapt to a new pathway called gluconeogenesis

- Gluconeogenesis allows new glucose to be produced using fats and amino acids as a starting point so the body starts to use the fat stores and the proteins in muscles to make the glucose that the brain and blood cells need.

- This explains why fat is lost and muscle wasting occurs during starvation

Where Glucose Comes From During Starvation



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Part 3
What happens when glucose homeostasis goes wrong ?

Diabetes

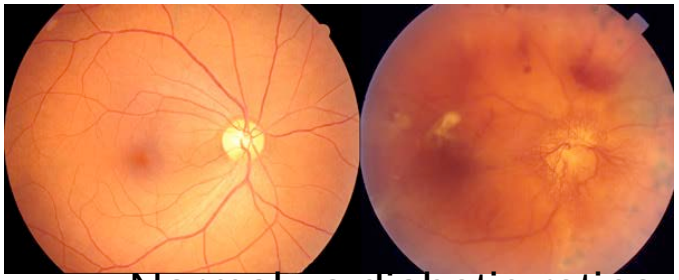
- Diabetes is the main disease that results in defects in glucose homeostasis. Strictly the full name for this is "Diabetes Mellitus".
- The word diabetes comes from the Greek word for siphon as they observed that people with diabetes urinated a lot (technical term is polyuria) and they thought that the body was siphoning water directly from the stomach.
- The word mellitus is from Greek word for honey and refers to the fact that the urine was sweet (don't ask how they knew this !). We now know this is because the urine contains a lot of glucose.
- NOTE - There is another form of diabetes (i.e. a disease characterised by polyuria) that does not have sweet urine, hence this form is called diabetes insipidus. It is caused by a defect in the kidneys. However, when people talk about diabetes they are nearly always talking about diabetes mellitus so for the rest of the presentation we will just call it diabetes.

What Happens in Diabetes (Mellitus)

- When blood glucose levels increase above 20 mM the kidneys can't retain it all and so glucose starts to spill over into the urine
- Once glucose levels in the urine rise it creates an osmotic imbalance (remember Year 12 biology) and so extra water starts to flow from the blood into the urine to compensate. That's why there is excessive urine volume.
- As a result the water levels in the blood fall which stimulates a a need to replace the water i.e. thirst. Excessive thirst (technical term polydipsia) is a consequence. This is another symptom of diabetes.

Consequences of High Blood Glucose for a Long time (Also Known as Diabetic Complications)

- Damage to small blood vessels that resulting in damage to retina (retinopathy) which leads to blindness.
- Damage to small blood vessels also causes problems with peripheral circulation so persistent infections and gangrene can set in.
- Damage to nerves (neuropathy).
- Damage to kidneys (nephropathy) – diabetes is the biggest cause of people requiring dialysis.
- An increased rate of development of coronary artery disease (atherosclerosis) – heart attacks are a major killer of diabetics.



Normal vs diabetic retina

Dialysis

Foot ulcer

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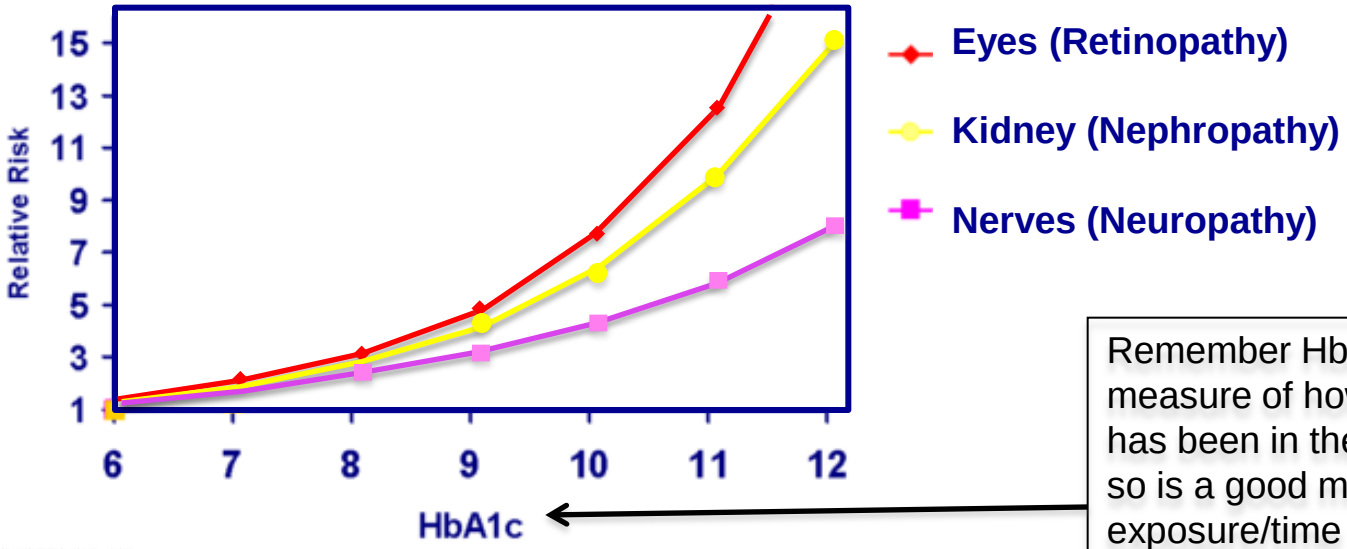
There is Now Strong Experimental Evidence That Keeping Blood Glucose Levels Low Reduces Incidence Of Diabetic Complications

Some of the most important evidence comes from a very large study of Type-1 diabetics in the USA which monitored the glucose levels in patients and compared it with the incidence of diabetic complications. This was called the Diabetes Control and Complications Trial (DCCT).

DCCT: Relative Risk of Progression of Diabetic Complications by Mean HbA1c



Remember HbA1c gives a good measure of how much glucose has been in the system over time so is a good measure of glucose exposure/time

Skyler JS: Endocrin Metab Clin N Am 1996; 25:243-254

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What Causes Diabetes

•The cause of the unusually high glucose levels associated with diabetes mellitus is that insulin is not working properly.

•There are two major reasons this can happen
(a) Maybe there is no insulin present. This is what happens in Type-1 diabetes.
(b) Maybe there is insulin present but it is unable to function. This is what happens in Type-2 diabetes.

Type-1 Diabetes

- This disease happens when the β-cells that make insulin are destroyed by an autoimmune reaction so people with this disease have no insulin

- Even though the autoimmune destruction of the pancreas happens over several years, the actual disease symptoms appear quite quickly and are very dramatic.

- The disease mainly appears in young people with an average age of onset of about 12 years old.

- In New Zealand about 1 in 300 people are affected by this disease.

Treatments for Type-1 Diabetes

- The only way to treat it currently is to add back insulin

- Genetically engineered types of insulin have changed the amino acid sequence to provide either rapidly acting forms or forms that act over much longer times than natural insulin. This makes life much easier for diabetics.

- In the future it is hoped that artificial islets or transplantation of human islets or xenotransplantation of pig islets (as at Living Cell Technologies in NZ) might provide a longer term treatment for the disease

Even With Insulin it is Difficult for Type-1 Diabetics to Properly Control Their Glucose

Three reasons injected insulin is different from natural insulin

(1) its injected subcutaneously whereas normal insulin comes from the pancreas directly to the liver

(2) the injected insulin takes longer to act than the insulin secreted from the pancreas

(3) the β-cells are continually sensing blood glucose levels and so can release just the right amount of insulin whereas the patient just has to make a best guess

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Even With Insulin it is Difficult for Type-1 Diabetics to Properly Control Their Glucose

To much insulin means very low glucose levels (known as hypoglycemic episodes) whereas if not enough insulin is used then blood glucose levels can rise to dangerously high levels (hyperglycemia).

A type 1 diabetic child injecting himself with insulin

Knowing what blood glucose levels are is very important if patients are to be able to judge whether they are using the right amount of insulin. This was impossible for the patient to do themselves at home until 20 years ago when miniature glucose meters were invented. This has revolutionised the way diabetics can control their disease.

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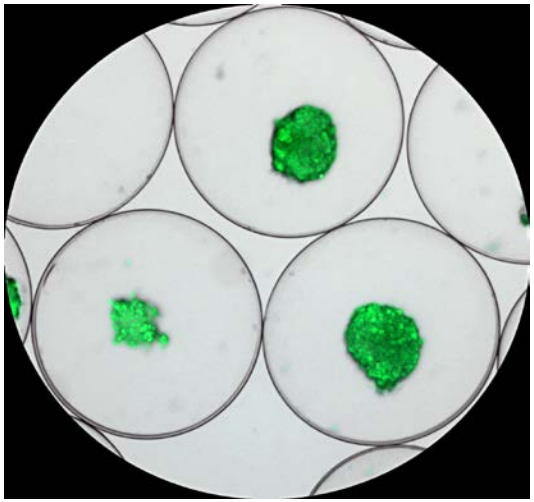
Xenotransplantation and Diabetes

- Living Cell Technologies in Auckland is trying to use pig islets to replace defective human islets as a way to treat Type-1 diabetes
- The advantages of their approach are:
  (1) They have a unique disease free herd of pigs from the Auckland Islands.
  (2) They encapsulate the islets with an alginate that lets small molecules such as glucose in to the cells and small hormones such as insulin to leave but blocks the larger molecules of the immune system such as antibodies from reaching the islets. This means the patients do not have to be on severe immunosuppressive therapies like they are in the case of human islets transplants

Auckland Island Pigs



Encapsulated Islets

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Insulin as a Therapy

- Before 1920s Type 1 diabetes meant certain death
- It was known from 1880s that the was something made in the pancreas that could control blood glucose but efforts to identify it were unsuccessful until 1921 Canadian scientists Fredrick Banting and Charles Best managed to find a way to purify the active material.
- Within a year this was being used in humans purified from the pancreases of pigs and cows and being used to treat diabetics.
- It was a miracle cure and has saved the lives of millions
- Things got even better in 1980's when insulin gene was cloned and insulin was the first protein produced by genetic engineering.
- In 1990's genetic engineering was used to alter the insulin to make forms that act more quickly or more slowly to meet the needs of diabetics.

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What Happens if Type-1 Diabetes is Untreated – Why Do People Die of This Disease ?

- Without insulin glucose can't be taken up into muscle, liver and fat so blood glucose levels will rise to very high levels and spill into the urine
- Fat uptake and storage into fat cells is also compromised as insulin is required for this so levels of lipids are very high in the blood
- Since these tissues can't use glucose they start using fats and amino acids as an energy source for these tissues instead so eventually muscle and fat tissues waste away. People suffering in this way look like they are starving even though they are getting plenty of food.
- To make things worse, when the body uses to much fat for energy it produces by-products called ketone bodies which build up in the blood and can actually be smelt on the breath of badly controlled diabetics (the smell of nail polish remover)
- These ketone bodies are acidic so as they build up they will acidify the blood which is physiologically dangerous. People who have this are described as being "keto-acidodic".

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Chemistry of Glucose Meters

- The chemistry which allows glucose meters to work might make an interesting chemistry project ?
- There is a very interesting and readable article available free online by Clarke and Foster in British Journal of Biomedical Science (2012) Vol 69 p83 which describe the history of chemical methods to detect blood glucose

Societal Issues- Potential Debate Topics

How Do We Deal With Impact of Obesity and Western Diet ?

- Will diet advice work ?
- Should we ban certain food in schools?
- Should we do more PE is schools
- Some people say we should make McDonalds and other have plain packaging like cigarettes (of course fish and chips already do but it doesn't stop people eating them)
- Some say we should we tax fast food like we tax cigarettes but cigarettes are not essential for life while food is so we might we be unfairly punishing everyone.
- How much do you need to over eat to get fat ? Think, only one extra 10g French fry per day would result in more than 3.5kg weight gain per year !! This means you really only have to eat a tiny bit to much to get fat.

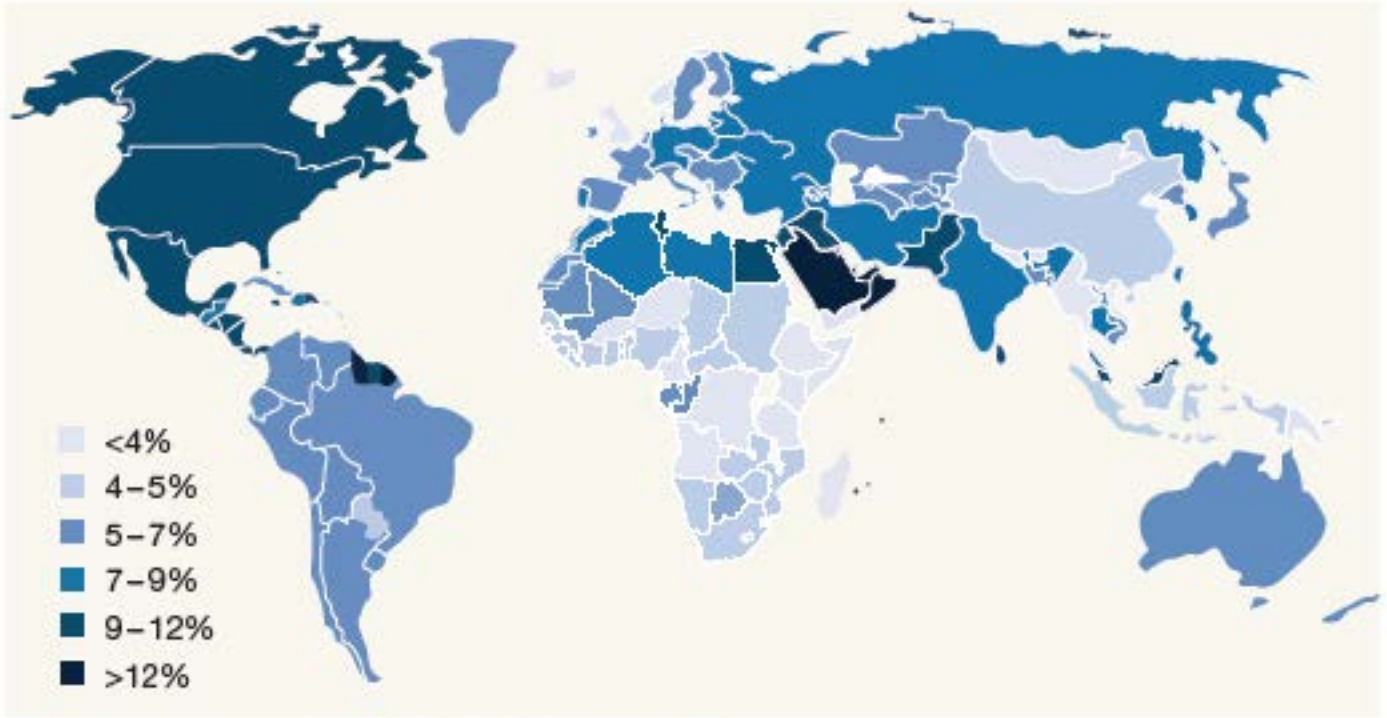
Type-2 Diabetes

- Unlike Type-1 diabetes, the symptoms develop slowly over a long period of time and may include polyuria, polydipsia, unexpected weight loss and unexplained tiredness.

- Unlike Type-1 diabetes, it usually occurs in older people and there is no association with autoimmune disease.

- The incidence of Type-2 is rising dramatically worldwide and is linked with westernised diet and lack of exercise.

Type-2 Diabetes is More Common in Rich Countries: Links With Lifestyle and Diet



Current global rates of diabetes (percentage of population)

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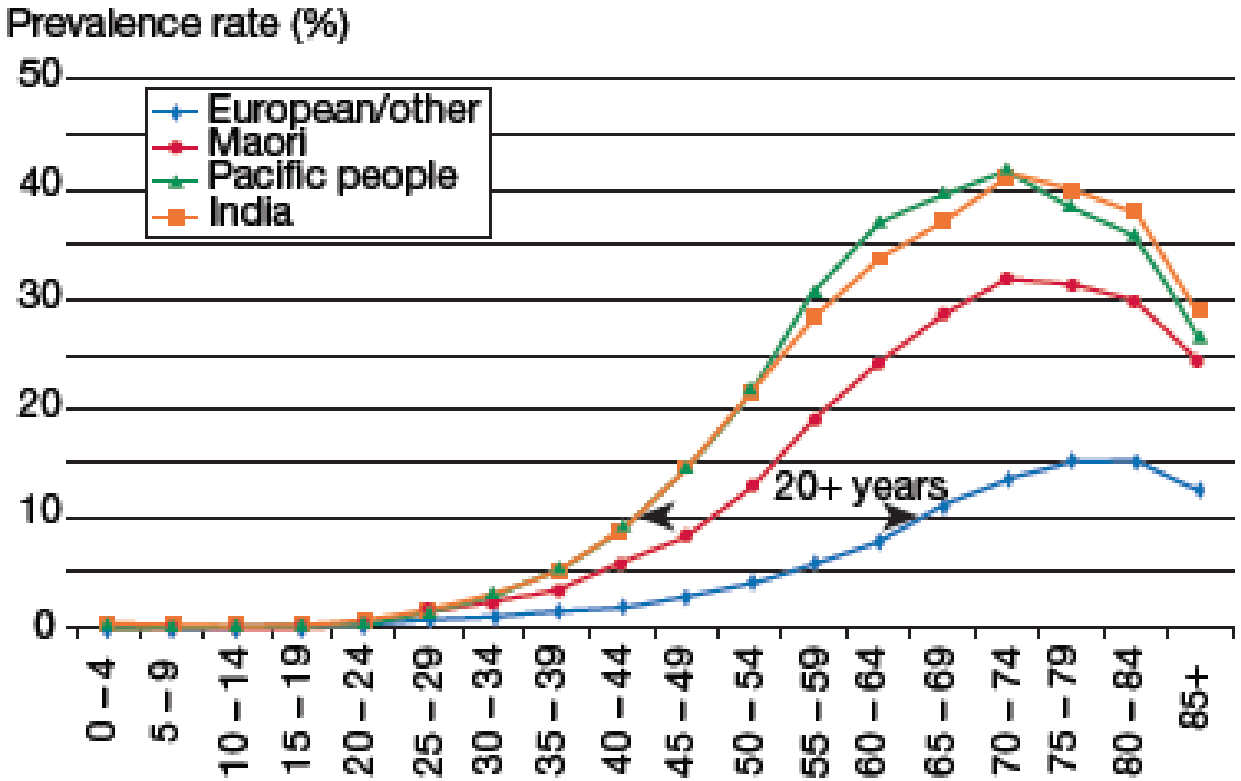
Prevalence of Type-2 Diabetes Higher in Older People and in NZ is Higher in Certain Ethnic Populations



tes prevalence rates in New Zealand, 2010

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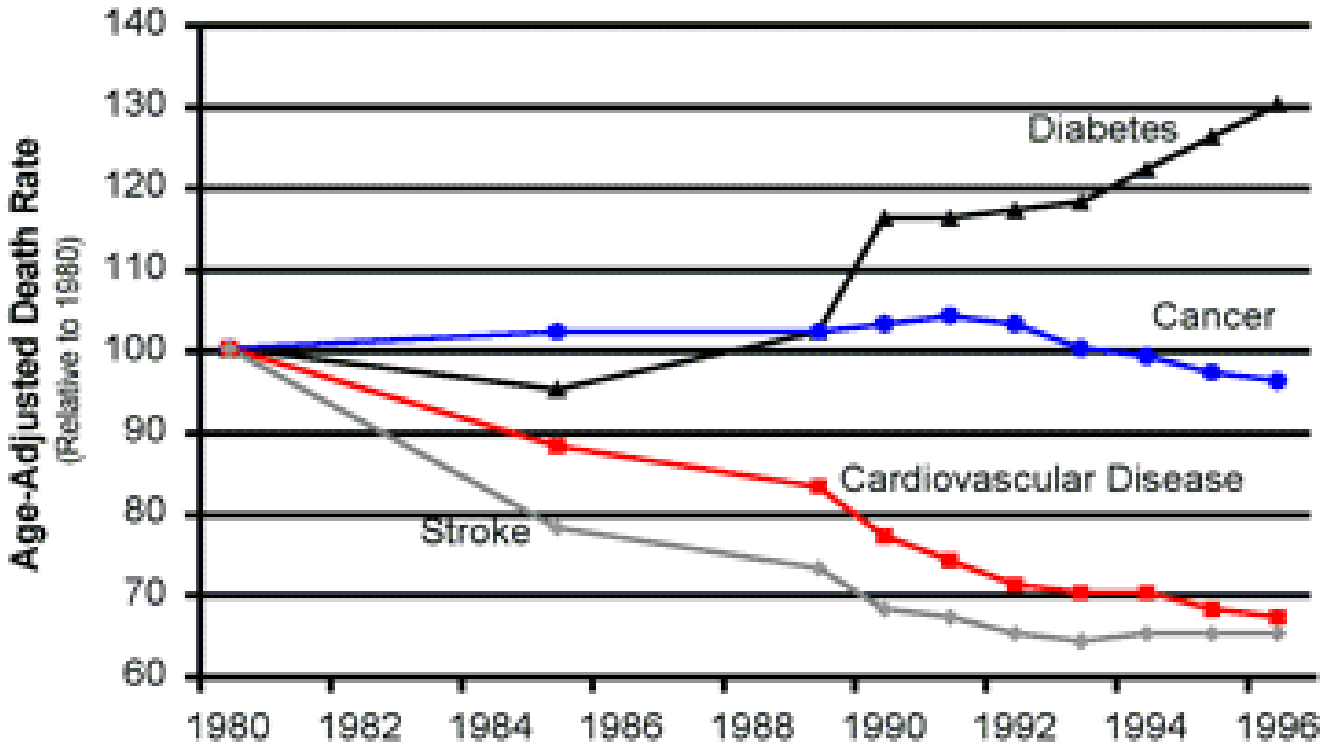
Type 2 Diabetes is the Only Major Disease on the Increase



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Causes of Type-2 Diabetes

- **Insulin Resistance:** Type-2 diabetes is nearly always preceded by many years where the insulin in the body is not able to function properly so glucose levels rise a bit. This is called “insulin resistance”. Over many years this can get worse and worse until it is full blown diabetes.

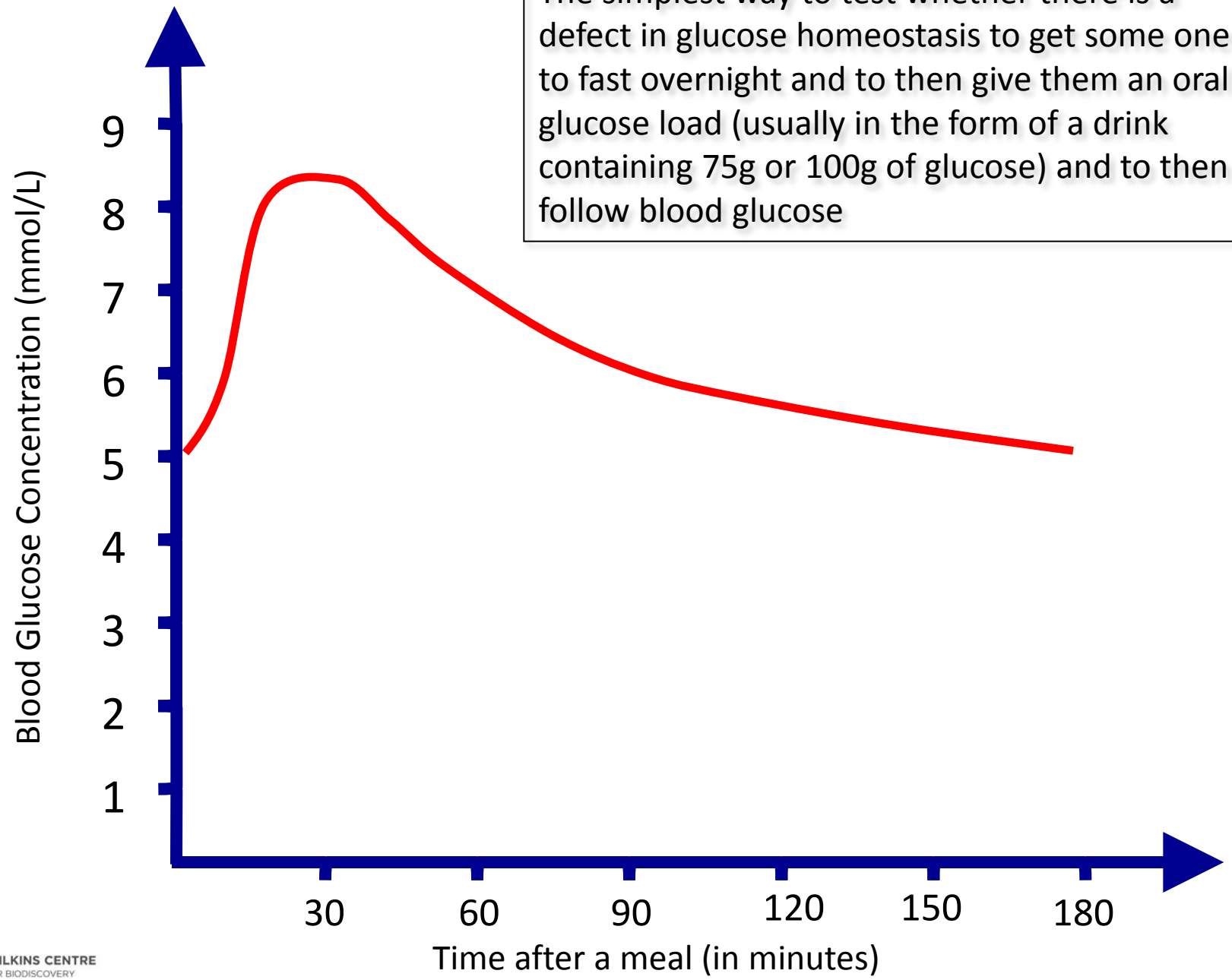
- **Obesity**: Obesity causes the development of insulin resistance so greatly increases the chances of getting Type-2 Diabetes. This is because lipids in the blood and some hormones made in fat cells can cause insulin resistance.

- **Genetics:** Not all people with obesity and insulin resistance will get diabetes, in fact only about 25% of obese people do – why is this ? Recent large scale genomic studies indicate that some people are predisposed to diabetes by having genetic predisposition to having defects in β-cells and these are the people who get diabetes.

How do we know someone has Type-2 Diabetes

- The simplest way to test whether there is a defect in glucose homeostasis to get some one to fast overnight and to then give them an oral glucose load
- This is usually in the form of a drink containing either 75g or 100g of glucose and to then follow blood glucose levels.
- This is called an oral glucose tolerance test (or OGTT)

The simplest way to test whether there is a defect in glucose homeostasis to get some one to fast overnight and to then give them an oral glucose load (usually in the form of a drink containing 75g or 100g of glucose) and to then follow blood glucose



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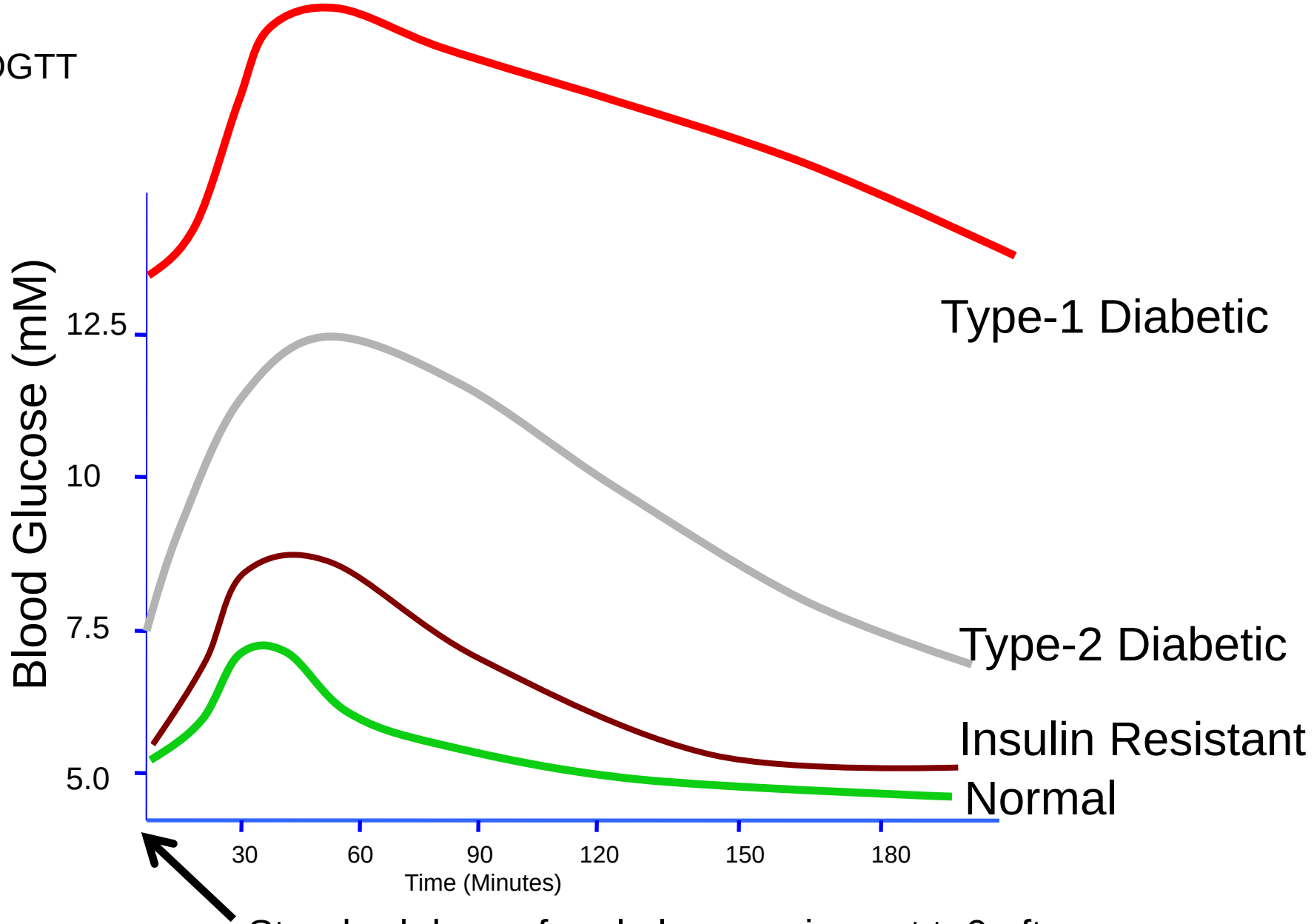

Standard dose of oral glucose given at t=0 after an overnight fast. Typically this is 75g of glucose in a drink form

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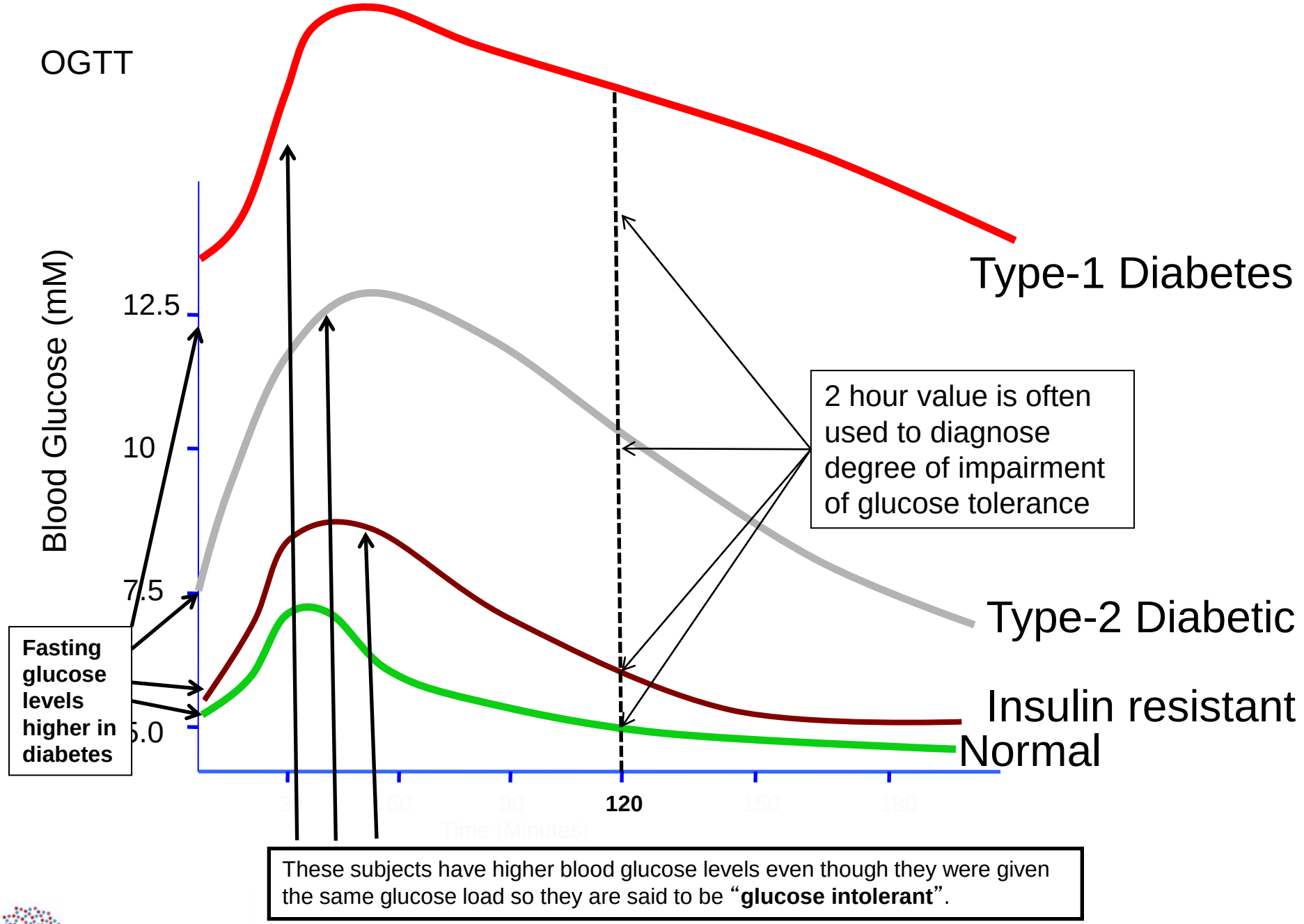

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What Can We See From OGTT

- Type-1 Diabetics have very high blood glucose levels all the time because they have no insulin

- Type-2 diabetics and insulin resistant subjects still have some ability to control blood glucose levels but the glucose levels are still higher than normal (i.e. they are said to be glucose intolerant) and so have the potential to cause serious damage and for diabetic complications to develop.

Type-2 Diabetes Diagnosis

Official diagnosis of diabetes if;

- A random plasma glucose concentration ≥11.1 mmol/L;
- **or** a fasting plasma glucose concentration ≥7.0 mmol/L;
- **or** two-hour plasma glucose concentration ≥11.1 mmol/L two hours after 75 g glucose in an oral glucose tolerance test (OGTT)

But if you are only just below this you are not safe as your blood glucose levels are still higher than normal !!

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Treatments for Type-2 Diabetes

First Line of Defense - Diet and Exercise

•The first line of therapy is to reduce food intake as excess food intake is part of the cause of the insulin resistance.

•Concurrently the recommendation is to exercise. Partly this is to reduce weight but it is also because exercise stimulates glucose to be taken up in to muscle by moving glucose transporters to the plasma membrane. This is just like insulin but uses a different mechanism that is fully operational in the insulin resistant condition. This means exercise can lower blood glucose independently of insulin.

Wayne from Diabetes NZ Rotorua Branch organises group walks every Wednesday morning for diabetics

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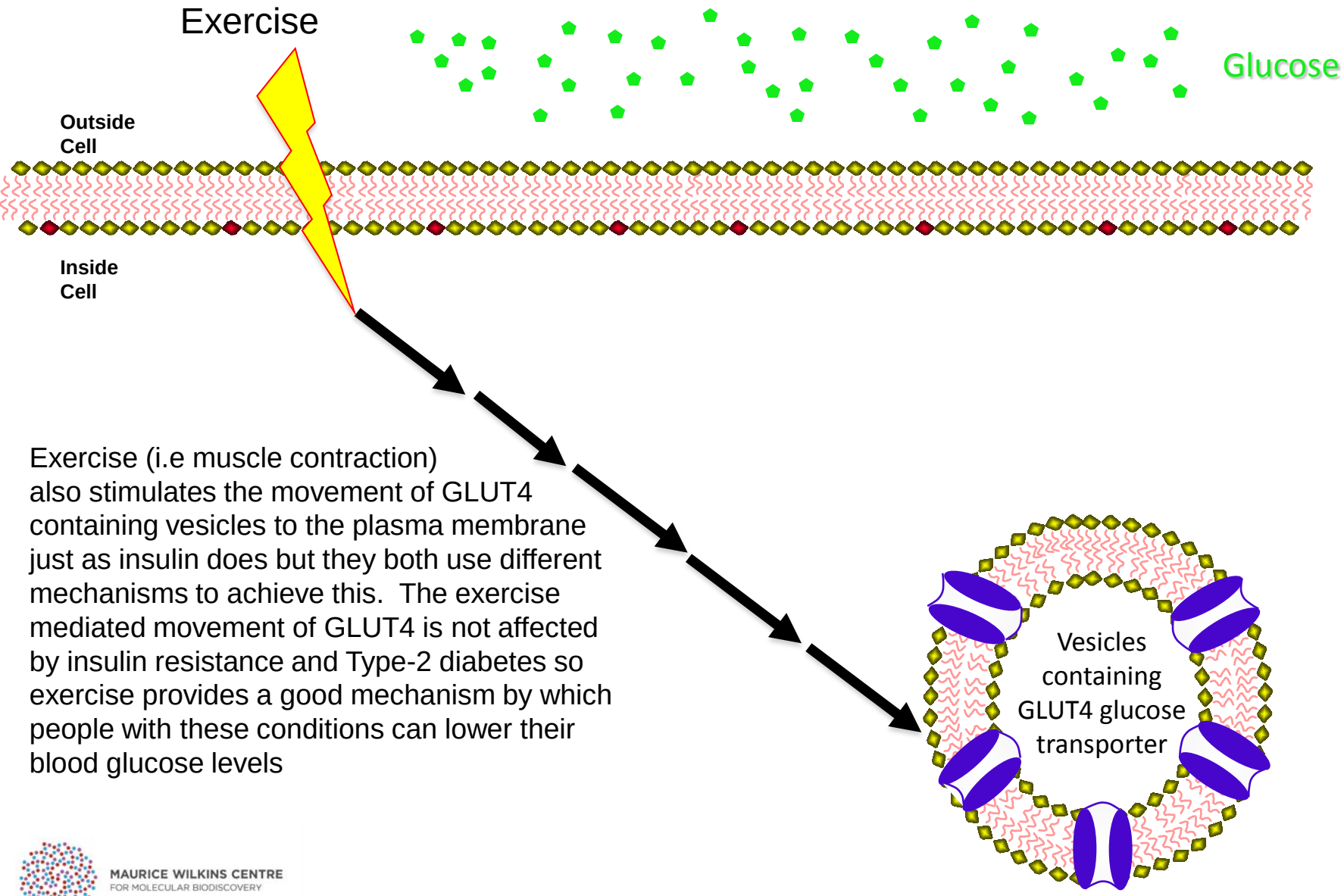
Exercise Stimulates Glucose Uptake Into Muscle (not fat)



Exercise (i.e muscle contraction) also stimulates the movement of GLUT4 containing vesicles to the plasma membrane just as insulin does but they both use different mechanisms to achieve this. The exercise mediated movement of GLUT4 is not affected by insulin resistance and Type-2 diabetes so exercise provides a good mechanism by which people with these conditions can lower their blood glucose levels

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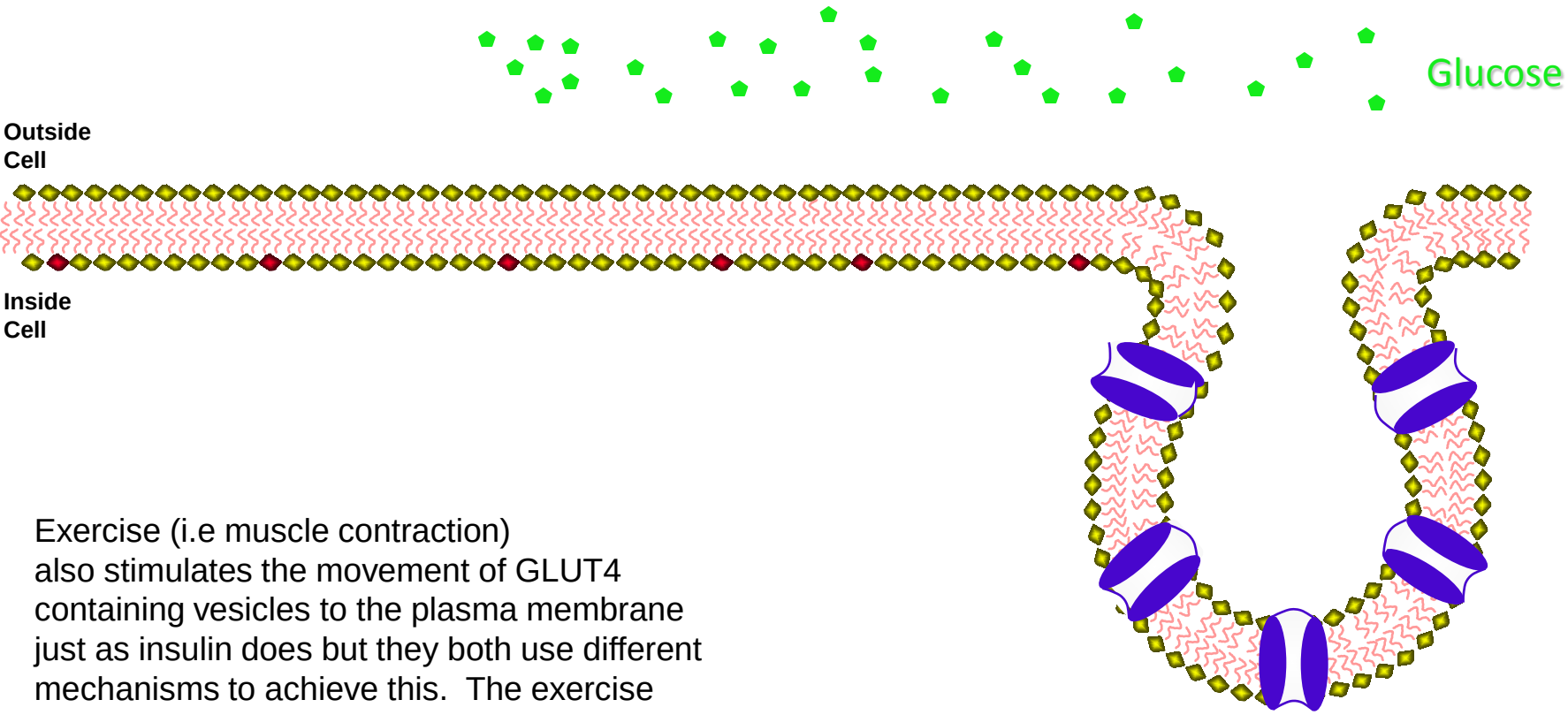

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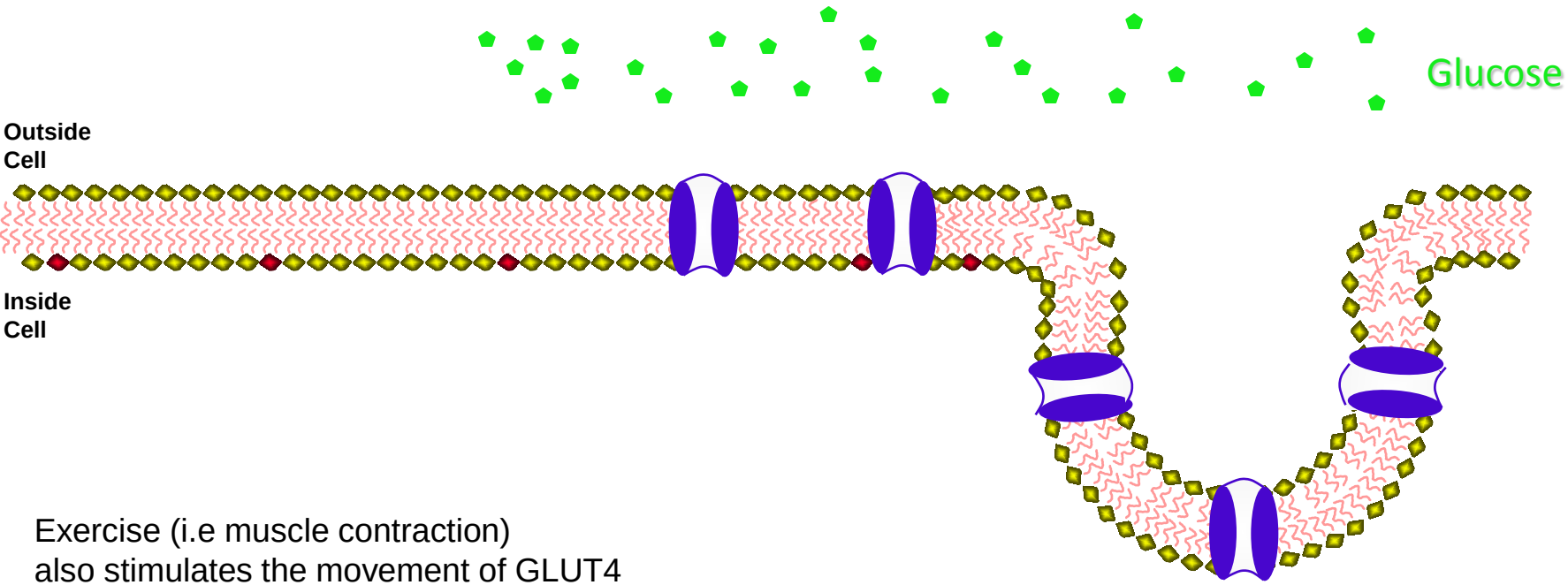

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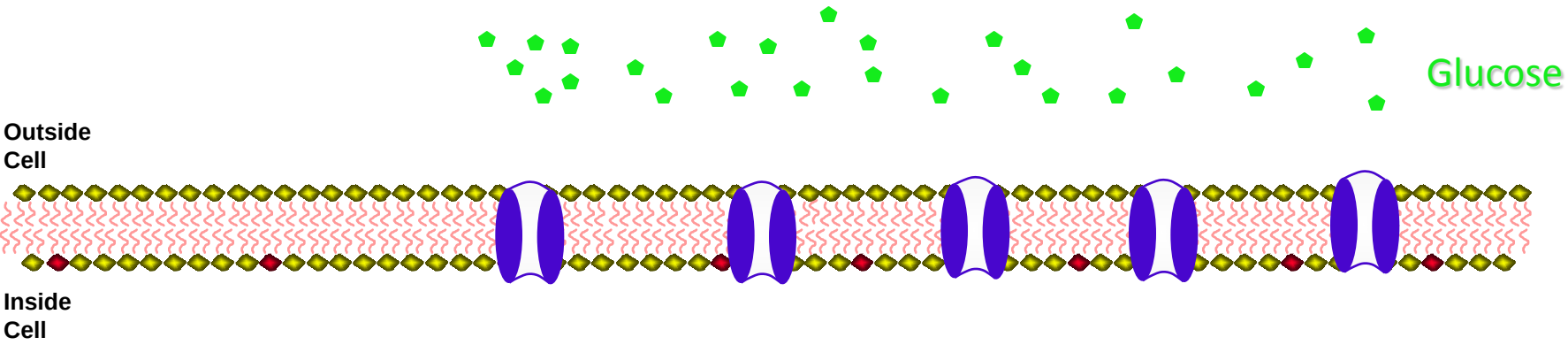

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Treatments for Type-2 Diabetes

Second Line of Defense is Drugs

•Sulfonylureas. These are a class of drugs that increase the amount of insulin in the circulation by making the pancreas secrete more.

•Metformin. This improves insulin resistance

Final Option

- Insulin injections

Treatments for Type-2 Diabetes

The future – Gastric Bypass Surgery

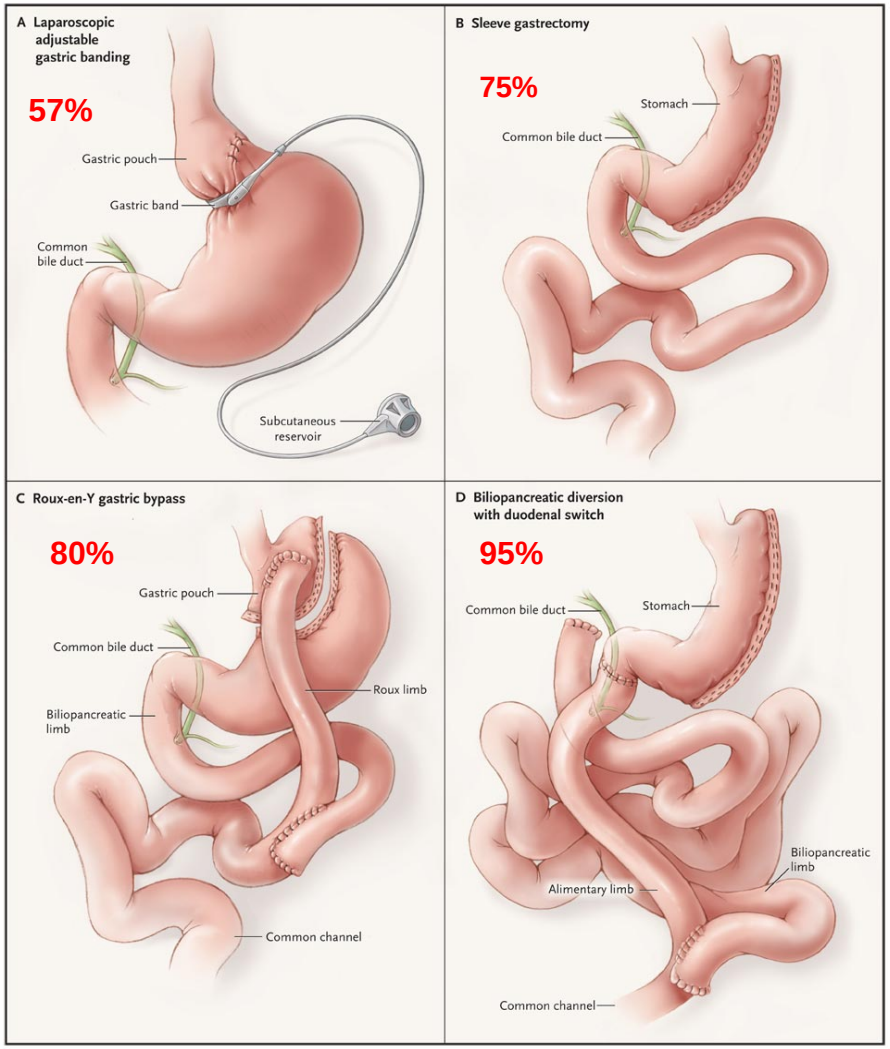
- Gastric bypass surgery was originally used as a method for bring about weight loss but it has recently been found that it also has independent effects on improving diabetes even *before* weight loss even starts. Therefore the surgical rerouting of gut seems to be curing the diabetes so there is huge interest in why this happens and whether surgery might be used more routinely to treat this disease.

- The effects of the surgery seem to be due to changes in the levels of hormones that are normally made in the gut. Maybe this is why it cures diabetes ?

- Over the longer term the weight loss will certainly help maintain a diabetes free state. The surgery also often changes peoples food preferences so they don't like fatty foods anymore. This probably also helps reduce insulin resistance.

- The down side is that surgery is expensive and can be dangerous in obese people and for some times of surgery there will be an ongoing need to supplement vitamins and minerals due to reduced bowel area.

Different Types of Bypass Surgery Have Different Rates of Effectiveness in Inducing Remission of Diabetes



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THE END

Please feel free to use the slides for teaching with appropriate acknowledgement and contact me if you need more information
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